THE DEVELOPMENT AND VALIDATION OF A RESPIRATORY GUIDELINE FOR NURSES IN PRIMARY CARE IN SOUTH AFRICA

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For Michael, Kyla, Claire, Kirsty, Morgan, Joshua, Lebu, Emma, and Franklin.

TITLE PAGE

THE DEVELOPMENT AND VALIDATION OF A RESPIRATORY GUIDELINE FOR NURSES IN PRIMARY

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ABSTRACT

The development and validation of a respiratory guideline for nurses in primary care in South Africa (Dr René English; August 2006)

The Practical Approach to Lung Health in South Africa (PALSA) initiative aims to improve the diagnosis and management of patients with respiratory diseases in primary care. An algorithm-based syndromic guideline integrating common respiratory diseases for nurses was developed after review of a generic respiratory guideline, medical literature, local policies, and qualitative research.

The diagnostic performance of the guideline was tested prospectively by comparing assessments made by a nurse using the guideline with those of physicians with access to special investigations in 1392 consecutive patients attending a primary care clinic in Cape Town. Patients ≥ 15 years with cough and/or difficult breathing were independently assessed (blinded) by (1) a nurse using the guideline (2) a primary care physician with access to detailed clinical information, spirometric data and chest radiographs, and (3) a respiratory physician who reviewed the data collected by the primary care physician. Only patients viewed by the latter who required screening for tuberculosis, underwent sputum examination. The subjects, 63% of whom were females, had a mean age of 48 years; 38% had asthma, 29% chronic obstructive lung disease, 26% acute exacerbation of obstructive lung disease, and 37% suspected tuberculosis. The performance of the nurse using the guideline was judged as good with sensitivities ranging from 33-90% and specificities from 65%-94%. Potential for resulting in harmful incorrect diagnoses was limited and outweighed by potential benefits of earlier diagnosis and institution of appropriate treatment, and/or appropriate referral to a higher level of care.

It is concluded that PALSA, a simplified guideline adapted for local conditions in primary care in South Africa, has satisfactory diagnostic accuracy for use by a nurse and may improve the service offered to patients with acute and chronic respiratory diseases in resource-poor settings.

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ABBREVIATIONS

AB	Dr Angeni Bheekie
AH	Dr Agnes Hurter
ARUC	area under the receiver characteristics curve
BHR	bronchial hyper-responsiveness
RDP	reconstruction and development plan
BM	Dr Bosielo Majara
BMI	body mass index
CHD	Child Health and Development
COPD	chronic obstructive pulmonary disease
DALYS	disability-adjusted life years
DOTS	Directly-observed therapy short course
EDB	Professor Eric Donn Bateman
EDL	Essential Drugs List
FET	forced expiratory time
FEV1	Forced expiratory time in 1 second
FS	Free State Province
FVC	Forced vital capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HIV/AIDS	human-immunodeficiency syndrome /acquired - immunodeficiency syndrome
IUATLD	International Union Against Tuberculosis and Lung Disease
JAMA	Journal of the American Medical Association
L/min	litres per minute
LF	Dr Lara Fairall
LR-	negative likelihood ratio
LR+	positive likelihood ratio
LRTI	lower respiratory tract infection
MFZ	Dr Merrick Zwarenstein
mmHg	millimeter mercury
MOB	Professor Max Oscar Bachmann
NICE	National Institute of Clinical Excellence
NPV	negative predictive value
OAD	obstructive airways disease
PAL	Practical Approach to Lung Health
PALSA	Practical Approach to Lung Health in South Africa
PHC	primary health care
PPV	positive predictive value
RD	Dr Rodney Dawson
RGE	Dr René Glynnis English
ROC	receiver operating characteristics curve
Sens	sensitivity

SIGN	Scottish Intercollegiate Guidelines Network
SN	Mrs Sharmladevi Naidoo
Spec	specificity
STG	Standard Treatment Guidelines
Stop-TB	Stop-Tuberculosis
TVR	Dr Tracy van Rensburg
UNICEF	United Nations Childrens Fund
URTI	upper respiratory tract infection
VCT	Voluntary Counselling and Testing

Chapter 1 : INTRODUCTION

1.1 Introduction

The aims of this thesis are two-fold. The first aim is to present the development methods and the final draft of the PALSA (Practical Approach to Lung Health in South Africa) guideline. This guideline is an algorithmic, symptom and sign based document that integrates respiratory diseases commonly encountered in primary care. The second aim of the thesis is to present the methodology and results of a validation study in which the accuracy of the PALSA guideline in diagnosing these respiratory conditions is assessed.

To provide a background to the work presented in this thesis, this chapter will briefly overview the burden of respiratory diseases both worldwide and locally, as well as the role of multipurpose health care workers in providing primary care. Thereafter, the World Health Organisation's (WHO) Practical Approach to Lung Health (PAL) strategy will be introduced. This will be followed by a description of the South African adaptation of this strategy, the PALSA initiative. Three literature reviews have been undertaken. These will provide an overview of primary health care in South Africa and the role of the nurse; the origins and evolution of guideline development; and finally; a review of the symptoms and signs that best predict obstructive airways disease in patients with respiratory symptoms.

1.2 The global burden of respiratory diseases

Respiratory diseases constitute about one-fifth of the global burden of disease as measured in disability-adjusted life years (DALYs),[1] and are among the leading causes of deaths.[2] In 2001, the largest contributors in this category in developed countries were chronic obstructive pulmonary disease (COPD), respiratory cancers (trachea, bronchial, and lung cancers), and asthma[3]; the first two contributing 7.1% to the total burden. In

contrast, in developing countries, tuberculous and non-tuberculous lower respiratory tract infections (LRTIs) are the leading causes of death and disability in both young and old, contributing 6% and 2.6%, respectively.[3] However, urbanisation and economic transition are resulting in a steady rise in non-communicable diseases such as asthma and COPD.[4] By 2020, tuberculosis will account for 31% of DALYs worldwide, followed by LRTIs (28%), and COPD (25%). In that year, LRTIs, COPD, tuberculosis, and respiratory cancers will rank among the top ten causes of death worldwide.[5]

1.2.1 Asthma

Over the last four decades the prevalence of asthma has increased by 50% every ten years.[6] These increases have been highest (>10%) in western countries. Although data for developing countries are limited, marked increases in Africa, Central and South America, Asia and the Pacific regions have been reported. This rise is partly attributable to increased exposure to indoor and outdoor pollutants, allergens, and tobacco smoke.[7] Globally, about 300 million people have asthma, of which 50 million are in Africa. In parallel to the rise in prevalence is an increase in hospitalisation due to asthma, which may reflect an increase in disease severity.[8 9] Despite improvements in overall asthma mortality rates over the past two decades, asthma still accounts for an estimated 180 000 deaths each year. Most of these deaths are thought to be preventable and represent inadequate or inappropriate care. For the year 1994, the direct global costs of asthma surpassed those for tuberculosis and HIV/AIDS combined,[10] and most of the economic burden of asthma is incurred by the relatively smaller number of severe cases.[9 11 12]

1.2.2 Chronic obstructive airways disease

The prevalence of COPD is estimated to be between 4% and 9% globally, and has been rising worldwide.[13 14] In men, the prevalence rate is estimated to be 9.33 per 1000 and for women, 7.33.[15] It is projected that COPD will rank fifth as a cause of death and disability by 2020.[5] In the United States, the prevalence of chronic bronchitis rose from 3% to 5%

between 1970 and 1993,[16] whereas estimates for developing countries suggest much higher prevalences (13-27%).[17] This rise is partly related to the increase in COPD risk factors (such as indoor and outdoor pollution and smoking), and the effects of ageing populations. It is greatest in developing countries where women and young people are starting to smoke at a younger age and more heavily.[18] Estimations suggest that between 15% and 50% of smokers develop COPD.[19 20 21] Worldwide, the number of deaths including COPD attributable to tobacco is expected to increase from 3.0 million in 1990 to 8.4 million in 2020, and it is predicted to be the leading cause of mortality compared to any other single disease.[5]

1.2.3 Tuberculosis

Tuberculosis is the leading potentially curable infectious cause of death worldwide.[22] The WHO reports that in 2004, 9 million (140 per 100 000) new cases, 4 million (62 per 100 000) smear-positive cases, and approximately 2 million deaths were reported.[23] More than 80% of new cases were from South-East Asia (35%), Africa (24%), and the Western pacific (24%). Although the global treatment success rate was excellent (82%; with a target of 85%), the case-detection rate was only 53%, falling far short of the 70% target. Despite these statistics, global trends indicate that overall the tuberculosis prevalence rate has decreased from 297 per 100 000 to 229 per 100 000 between 1990 and 2004. Incidence rates have also stabilised or fallen in 6 of the 9 epidemiologically different WHO regions (1.2% per year in 1997 to 0.6% per year in 2004). However, this has not been the case in sub-Saharan regions, where the HIV epidemic has fuelled a dramatic rise, both in tuberculosis and other respiratory diseases.[24 25 26] By 2020, HIV and AIDS, will be the 9th leading cause of deaths worldwide and will contribute 39.7% to the overall global burden of disease.[5]

1.2.4 Acute respiratory infections

In total respiratory tract infections account for large numbers of deaths,[27] but the contribution made by upper respiratory tract infections (URTIs) to these deaths are much smaller owing to their short duration, self-limiting nature and milder morbidity. LRTIs accounted for 7% of the total deaths in low-and-middle-income countries in 2001, and 4.4% in high-income countries.[3] It ranked third in the former and fourth in the latter. By the year 2020, LRTI will contribute 28% to the total burden of disease and will be the fourth leading cause of death worldwide.[5]

1.3 The burden of respiratory disease in South Africa

Data on the burden of respiratory diseases in South Africa is limited. But a recent comprehensive study reported that the pattern of respiratory diseases in South Africa is mixed, comprising poverty-related conditions such as lower respiratory tract infections, the effects of HIV/AIDS, and emerging chronic diseases.[28] Respiratory diseases rank eighth and respiratory tract infections ninth as causes of death, and are exceeded only by HIV and AIDS, other infectious conditions, cardiovascular diseases, malignancies, injuries, and perinatal conditions. They are also major causes of premature mortality (years of life lost). The HIV/AIDS epidemic is expected to more than double the burden of premature mortality by 2010, and is predicted to add to the existing burden of disease in all 9 provinces of South Africa (see Appendix 1 for a map of South Africa).[29] In all but one province (Kwa-Zulu Natal), COPD is among the top 20 causes. The incidence of tuberculosis is amongst the highest in the world (718 per 100 000 population per year) with 135 deaths per 100 000 population per year,[23] and with a tuberculosis and HIV co-infection rate exceeding 60%.[25]

In the National Demographic Household Survey conducted in 1998, it was established that approximately 7 million South Africans smoked.[30] The prevalence of self-reported

asthma for males and females were 3.7% and 3.8%, respectively; for emphysema, they were 4.2% and 4.8%, respectively. Asthma symptoms were reported in 6.7% of males and in 8.6% of females, and chronic bronchitis symptoms ranged from 2.3% to 2.8% for the two sexes. Low socio-economic communities comprising most of the countries' population are most affected by respiratory disease. These communities also traditionally have less access to health care and other necessary resources. Asthma symptoms, lower peak expiratory flow rates, chronic bronchitic symptoms, tobacco smoking, and domestic use of biomass fuels were strongly correlated with levels of education and illiteracy. Another study of adult medical admissions to a rural South African hospital (1991-2002) reported that respiratory diseases are the most common reasons for presentation.[31] Tuberculosis (37%) and LRTIs (15%) are the most common indications for admissions, and the most frequent causes of death. These results reflect the increased burden of communicable and non-communicable respiratory diseases encountered in a country undergoing epidemiological transition.

1.4 Respiratory diseases in primary care in developing countries

Cough, dyspnoea, and sputum production are common symptoms in primary care and are often acute.[32 33] It is estimated that up to 30% of patients presenting to primary care in developing countries have respiratory conditions.[34 35] There is however a paucity of data on the prevalence of respiratory conditions in primary care in developing countries.[34] Thus, to address this deficiency, a multi-country evaluation of respiratory conditions among 29 000 patients age 15 years and older presenting to 76 primary care facilities was undertaken by the World Health Organization.[34] Respiratory tract infections were shown to account for 90% of all presentations, with upper respiratory tract infections being much more common than lower respiratory tract infections. Pneumonia accounted for only a small percentage. In this survey, the proportion with chronic respiratory diseases ranged from 2-25%. Tuberculosis was a consideration in 40%, and sputum examination was indicated. However, of these suspects, less than 5% were actually proven to have

tuberculosis. Respiratory drug prescription was high (95%) with between 50-75% receiving antibiotics, most of which on review were thought to not be indicated.

1.5 The role of multipurpose healthcare workers

In most primary health care settings throughout the world, first-level facilities are staffed by multipurpose healthcare workers.[36] These deliver a wide range of promotive, preventive and curative services, and are also faced with administrative duties like completing patient records, overseeing the running of the health facility, and ordering supplies. Protocols or standardised treatment policies are often not applicable to the local setting or are not integrated, leading to increased variation in care, and unnecessary expenditure of available resources due to inappropriate use.[37 38] In many countries, like South Africa, these facilities are staffed by nurses rather than doctors and the former often feel ill-equipped to fulfill all the responsibilities required of them.[39] Their task is made more difficult by limited access to diagnostic tests, financial constraints, and inadequate training and support from physicians, mentors and managers. Owing to a combination of the increasing burden of respiratory diseases worldwide, the consequent increase in the numbers of patients to be seen in primary care, as well as health sector reform, interventions aimed at integrating and improving the detection and management of respiratory diseases should be targeted at first-level facilities. Multipurpose primary health care workers are therefore well positioned to be the recipients of these interventions. Despite the obstacles faced by these health care workers, research shows that they are able to provide improved health care if trained to do so.[40 41]

1.6 The role of simplified interventions

Interventions for primary care should be simplified and tailored according to the level of training of the healthcare worker. 'Simplified' implies that the intervention promotes productivity through ensuring increased consistency of tasks and efficiency, often by lower cadres of health workers.[36] They should provide comprehensive care through

integrating the approach to patients with respiratory complaints, rather than focusing on a single disease. Interventions, such as primary care guidelines, should preferably be symptom and sign-based (syndromic) given the limited available diagnostic resources and capabilities, and should be implemented in as simple a manner as possible without interruptions of the daily workload. And finally, they should build on existing knowledge, complement existing local policies and guidelines, and should provide standardised recommendations based on evidence.

1.7 Initiatives to provide standardised interventions for respiratory diseases

In many developing countries the problem of managing respiratory diseases is aggravated by reduced quality and delivery of medical care,[42] inappropriate antibiotic and inhaled corticosteroid prescriptions,[43] underdetection of asthma, COPD and tuberculosis, [44 45] and non-adherence to guideline recommendations.[46 47 48 49] Other aggravating factors are the unavailability, or high costs of respiratory medications,[50] and the decreased status of respiratory diseases as a public health priority.[51] Over the past decade there has been a growing international interest in global initiatives aimed at standardising the management of respiratory conditions. Some like the Global Initiative for Asthma (GINA)[52] and the Global Initiative for Chronic Obstructive Disease (GOLD)[53] have focused on one disease, whereas others like the IUATLD[54] on several. These international agencies are actively engaged in addressing many of the above-mentioned problems, chiefly through technical advice and assistance in developing local responses to these needs. Other organisations like the World Health Organization (WHO) have emphasised the importance of improving and standardising the management of tuberculosis and other respiratory conditions worldwide.[55] One of the main identified barriers in achieving these aims however is the failure of many countries to adapt their guidelines to suit local health systems, practices, and resource availability.[56 57] Other challenges are finding effective ways of changing the behaviours of health care professionals.[58]

1.8 The Practical Approach to Lung Health (PAL) strategy

The PAL strategy[59] was developed by the WHOs Stop-TB Department to provide a comprehensive syndromic approach to adult patients presenting to first-level facilities in developing countries with respiratory conditions. A generic guideline that integrated the case management of asthma, COPD, tuberculosis, lower respiratory tract infections, and accompanying training materials for multipurpose health care workers, usually nurses, was developed. The guidelines also contained approaches to the management of malaria and HIV/AIDS. It is fully consistent with GINA, GOLD, the WHO Tuberculosis guidelines and the WHO Essential Drug List. Special emphasis was placed on including the most cost-effective interventions, and on including recommendations based on evidence.[60 61 62]

PAL was developed to be a component of the Global DOTS Expansion plan[63 64] and also of the new Stop TB strategy[65] in that it was developed to contribute to strengthening health systems, and to promote the participation and expansion of tuberculosis care to respiratory care. More focused aims are to increase the case detection of tuberculosis, and to provide diagnostic and treatment support for further investigation of patients who remain symptomatic despite having been shown to not have tuberculosis through bacteriological testing of their sputa. The initiative is based on the successes of other guideline development and implementation approaches, such as the Directly-Observed Therapy Short Course (DOTS)[66 67] programme and the Integrated Management of Childhood Illnesses (IMCI)[68] initiative. IMCI, a precursor to PAL, will be discussed in more detail in Chapter 3.

Requirements for optimal uptake of PAL are a well-functioning primary healthcare sector, a fully implemented national tuberculosis control programme, and governmental commitment to adapt, develop and implement the guideline and strategy. PAL has been implemented in a number of countries around the world, including South Africa, Morocco, Nepal and Chile[69] and has now been implemented to varying degrees in more

than 14 countries. The South African adaptation of PAL is known as the Practical Approach to Lung Health in South Africa (PALSA).

1.8.1 The PAL Guideline

Syndromic diagnoses are offered for patients presenting with cough and/or difficult breathing, and/or fever. Diagnostic and treatment algorithms are presented in 7 main sections: acute care of the sick adolescent or adult; follow-up care for acute illness; chronic care for all ages; laboratory tests; treatments; palliative care, and finally, advice and counselling. Guidelines for implementation at a national level were also designed. These guidelines were intended to be adapted to match individual countries' epidemiological and socio-economic conditions.

Through the use of the *Ask, Look, Listen* management plan (Appendix 2), the PAL guideline asks questions relating to the assessment of the duration, severity, and associated presenting features of the presenting illness. Through the *Classify* and *Identify Treatment* management plan, disease syndromes are grouped according to (1) the presence of wheezing (2) a previous diagnosis of COPD (3) no known history of COPD. The *Ask* section includes questions that cover the following history items: previous diagnosis of asthma, COPD, heart failure TB; age; smoking status with or without associated loss of weight; and use of medications; duration of the presenting respiratory symptoms; severity and frequency of those symptoms; and symptoms that predict asthma and COPD. The *Look, Listen* section includes assessment of the following examination variables: mental state of the patient; breath rate; degree of breathlessness; use of accessory muscles; inability to speak; ability to walk unaided. Other indicators are: wheezing; temperature and the presence of oedema. Many of the questions in the *Classify* section relate to the assessment of the severity of disease. Clinical indicators defining very severe, severe, moderate or mild disease are repeated in every section regardless of the final disease syndrome.

1.9 Development of the Practical Approach to Lung Health in South Africa (PALSA)

In 1999, the Department of Health of the Free State (FS) province of South Africa, approached the Medical Research Council's Health Systems Research Unit to request assistance with planning for improving services for patients with respiratory diseases in their province. PAL was suggested as a potential strategy for this purpose. Upon review, the FS province was considered ready for implementation of PAL as it had a functional tuberculosis control programme and a well-developed network of primary care clinics as well as provincial commitment to strengthen healthcare systems. However, it was evident that PAL would require considerable adaptation to make it suitable for local conditions and practices, including its use by nurse practitioners rather than by doctors. The first phase of implementation was therefore to adapt PAL to a local primary care respiratory guideline to be known as PALSA.

1.9.1 Objectives of the PALSA guideline development initiative.

The PALSA project team identified the following objectives:

1. To develop the guideline to address priority respiratory diseases in primary care clinics where nurse practitioners provide the 'frontline' care for patients with these conditions.

2. To identify and address perceived and actual barriers to the quality of respiratory disease care through brainstorming, focus group discussions, and consultation with frontline clinicians, key role-players and stakeholders.

3. To evaluate in a validation study, the performance of the PALSA guideline as a tool for diagnosing respiratory diseases and grading of disease severity; and for directing treatment of respiratory diseases.

4. To develop interventions aimed at improving the implementation of the PALSA approach, including a programme of in-service training.

5. To evaluate the effect of implementing the PALSA guideline and training approach in the field setting, by means of a pragmatic randomised controlled trial.[70]

1.10 The work reported in this thesis

This thesis therefore forms part of the larger PALSA intervention strategy aimed at evaluating the impact of the development and implementation of the guideline and other support materials through an in-service training programme (educational outreach) in a predominantly rural province, the Free State province, in South Africa. Other components of the larger project that are described briefly in the sections that follows are: (1) An evaluation of the effectiveness of the PALSA guideline in improving the way nurses identify and manage respiratory conditions in primary care assessed in a pragmatic clustered randomised controlled trial. This work formed part of the doctoral thesis of Dr Bosielo Majara (Free State University). (2) A study of the economic, cost-effectiveness, and quality of life outcomes of the PALSA intervention evaluated alongside the Free State randomised controlled trial. This forms the topic of the doctoral thesis of Dr Lara Fairall (University of Cape Town) submitted in August 2006. Finally, Mrs Pat Mayers (University of Stellenbosch) conducted qualitative research and evaluated the acceptability of the intervention to nurses. This work will be presented as part of her doctoral thesis.

Chapter 2 provides an overview of the origins and evolution of primary health care in South Africa, and a brief description of the role of the nurse in primary care. Barriers to comprehensive primary health care in South Africa will also be explored.

Chapter 3 of this thesis describes two emerging models of guideline development. The evolution of rigorous evidence-based guideline development methods, and then that of

more pragmatic syndromic, integrated guidelines, developed specifically for implementation in resource-poor settings will be discussed. An aim of this chapter is to provide background to the origins and development of the PAL strategy, the forerunner of the PALSA initiative

Chapter 4 presents a review of studies reporting the accuracy of clinical features (history-related information, symptoms and signs) in diagnosing obstructive airways disease.

Chapter 5 details the methods employed in developing the PALSA guideline, and **Chapter 6** presents the results of this process

Chapter 7 details the methods and materials for the validation study, in which the accuracy of the PALSA guideline in a primary care clinic was tested. **Chapter 8** presents the results of this study.

In **Chapter 9** the above results are discussed, together with the strengths and limitations of the study, and implication for primary care policies and future research.

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Chapter 2 : LITERATURE REVIEW: Primary Health Care in South Africa and the role of the nurse.

2.1 The concept of primary health care

The concept of primary health care arose as a result of a number of medical and political events in the 1960s and 1970s.[1] Criticism of verticalised programmes such as the malaria eradication programme run jointly by some North American agencies and the World Health Organisation (WHO) gave rise to a series of publications challenging the model of primarily hospital-based curative health care which excluded preventive care, particularly for developing countries.[2] In addition, the success of rural medical models which promoted community involvement in the provision of health care further served to provide support for a new model of care.[3] [4] [5] The International Conference on Primary Health Care at Alma-Ata in 1978 formalised the concept of primary health care and led to its adoption as a global strategy.[6]

2.1.1 The global introduction of the concept of comprehensive primary health: The Alma-Ata Declaration

The primary health care conference held in Alma-Ata, was attended by delegates from 134 countries and 67 international agencies.[1] It resulted in the approval of a document known as the Declaration of Alma-Ata which detailed the fundamentals of primary health care.[6] 'Health for all by the year 2000' was identified as a primary global target and primary health care was considered to be the means to achieving this goal.

In the Declaration document, primary health care was defined as[6]:

> essential health care based on practical, scientifically sound and socially acceptable methods and technology made universally accessible to individuals and families in the community through their full participation and at a cost that the community and country can afford to maintain at every stage of their development in the spirit of self-reliance and self-determination. It forms an

integral part both of the country's health system, of which it is the central function and main focus, and of the overall social and economic development of the community. It is the first level of contact of individuals, the family and community with the national health system bringing health care as close as possible to where people live and work, and constitutes the first element of a continuing health care process.

Eight of the ten statements of the Declaration can be summarised as follows:

- Health inequalities between developed and developing countries and within countries were considered to be unacceptable.
- Socioeconomic development was considered to be vital to the attainment of health with health promotion and protection being integral to socioeconomic development and improved quality of life.
- Community participation in the planning and implementation of their health care was considered to be the right and duty of each person.
- Governments have a responsibility to ensure achievement of the social target of health for all by the year 2000, and for ensuring socioeconomic productivity.
- Governments were to develop policies, and strategies to introduce and implement primary health care as part of a comprehensive national health system. This was to be done through intersectoral collaboration and mobilisation of internal and external resources.
- Countries should partner to ensure that each country benefits from the advancements of the other.
- World resources should be redirected from the support of wars to initiatives that promote peaceful aims, with it rightful share going to primary health care, and to the advancement of socioeconomic development.

2.1.2 Components of a functional primary health care programme

According to the Alma-Ata declaration, fundamental to the establishment of a functional primary health system is the successful integration of the above-mentioned factors and active collaboration between the various roleplayers with the formation of

a multidisciplinary health team. Health ("a state of complete physical, mental and social well-being"), is considered to be a basic human right. Re-organisation of health services with a focus on community-based, as opposed to hospital-based care and a shift from central to more peripheral services, in particular to the district level is fundamental to its success. The components of a successful primary health care programme are defined as equity, accessibility, affordability, availability, effectiveness, and efficiency. [7]

2.2 The history of primary health care in South Africa

The political history of South Africa has shaped the health care system, and understanding its evolution is integral to understanding why primary health care is structured and functions in the way that it does today. The fragmentation and inequality so evident during the apartheid years have, and continue to this day, to mark health care. In the early 20th century, health care provision in South Africa was haphazard and fragmented. The formation of the Union of South Africa in 1910 further fragmented the health system by creating independently functioning health systems in the various provinces.[8] Curative services provided by general hospitals dominated. [9] The passing of the Health Act No. 36 of 1919, which led to the establishment of the Department of Public Health, were in response to the devastating effects of the influenza epidemic in 1918. [10] The main thrusts of this Act were to improve health care in general by promulgating hospital-based health care and promotive and preventive medicine. But contrary to the intentions of the Union government to unite the health authorities through this Act, it merely led to further fragmentation of the health system.

The medical and social problems affecting the poor of all races in South Africa during the 1930s and 1940s, and the pro-World War 2 political strategies of the British colonists which promised health "benefits for all",[11] prompted the establishment of the National Health Services Commission, under the direction of Dr. Henry Gluckman. The commission reviewed international research on preventive medicine, and local health units and programmes, and produced the Gluckman Report,[12 13] which proposed the introduction of health promotion, prevention, curative care and

rehabilitative strategies in primary care. Significantly, it also proposed a national health system under the control of a minister of health, free health care for all, restraints on private practice, a well-functioning referral system, an increase in training of health professionals and the need for more governmental concern and responsiveness to the needs of the whole population. However with the election of the National Party Government in 1952, the South African Health Centre Programme came to an end, and so did the promise of health for all. By the mid-1960s all the health centres had been closed.[14]

The second wave of health care reform with suggestions to adopt a comprehensive primary health care approach occurred in the late 1970s in South Africa, mainly in response to economic recession.[8] The Health Act No. 63 of 1977 [15] served to emphasise preventive health care and to promote health care. Local authority clinics (community-based) were given the task of providing preventive, promotive and rehabilitative health care, and provincial administrations were tasked with the provision of curative care. Unfortunately the broader aims of this Act were never achieved. [16] [17] [18] More health care plans, [19] [20] [21] [22] intended to reinforce the implementation of primary health care were passed in the years that followed. The core elements of primary health care were included in these plans with decentralization and community-focused training of health professionals. However, lack of cooperation and uncertainty about financial resources for both provincial and local authority clinics prevented its implementation.[16] The Health Act of 1990 also proposed that users pay for services and that private health care continue to play a role in health service provision in South Africa.

2.3 The adoption and implementation of comprehensive health care in South Africa: post-1994

The democratisation of South Africa in 1994 provided scope for the introduction of primary health care and active promotion of the formation of the district health system.

2.3.1 Reconstruction and development programme: 1994

The Reconstruction and Development Programme (RDP) [23] of the new ruling party served as a framework for implementing equitable policies to improve socioeconomic conditions. The RDP document described how the health system in South Africa was to be transformed and contained all the elements of the Alma-Ata declaration. A more detailed plan was laid out in the National Health Plan for South Africa.[24] It proposed that the primary health care approach be adopted nationally and that services be brought 'into line with international thinking and practices'.[24] Community health promotion, prevention, curative and rehabilitative care were to be the focus. Efficient and appropriate referral of patients within this coordinated and integrated system was to be emphasised. The White Paper for the Transformation of the Health System in South Africa [25] and The Primary Health Care Package for South Africa – a set of norm and standards: 2000, [26] stated that an integrated package of essential primary health care services was to be made available to the population at the first point of contact. A free health service for children under the age of 5 years, pregnant women, and mothers was proposed and implemented. The prevention, early detection, and treatment of tuberculosis care was to be prioritised. Cost-effective essential drugs were to be made available at all primary care clinics, and an Essential Drugs List (EDL) and Standard Treatment Guidelines (STG) were to be established.

The role of health care workers was more explicitly defined. [25] Those working at primary care level were primarily responsible for providing health care services. The policy stated that[25]:

> there is a particular need to train existing and new staff in the primary health care approach, in management, in primary clinical care, in environmental health, in health promotion and advocacy, in occupational health and in the maintenance and repair of equipment.

It was evident that nurses would be expected to provide a wide range of basic services and that much of the responsibility for care in this transformed system would fall upon the shoulders of nurses - who form the backbone of primary health care.[27]

2.4 Nurses: the backbone of primary health care in South Africa

In 1994, nurses formed the bulk (60%) of health care professionals in South Africa, and about two-thirds worked within the public sector.[27] In theory, their basic training equips them for primary health care service delivery, but is not sufficient to prepare them for all the roles they were now expected to play.[28] Their training remains largely hospital-based and geared towards curative care with insufficient exposure to primary care teaching or practice, and with an orientation toward a doctor-driven model of care. Nurses are expected to know how to diagnose diseases, to recognise severe conditions, to exercise clinical judgment by knowing when to refer, to counsel, and to execute administrative tasks such as the recording of statistics and ensuring that equipment is fixed.[26] The nurse is also expected to seek training where lack of skills are identified, and in-service training is to take place on a regular basis.[29] [26]

The White paper for the transformation of the health system in South Africa requires nurses to provide the following primary health care services[25]:

- Promotive and preventive services that encompasses health education, family planning, immunisation, nutrition, and screening for common diseases.
- Curative care for minor acute conditions, communicable and chronic diseases, and trauma.
- Essential drugs.

- Basic optometry services, with appropriate referral when indicated.
- School and other institutional services including oral health, audiology, and optometry.
- Mental health and substance abuse services.
- Community nursing, home care, and palliative caring for the terminally ill.
- Geriatric services.

The White paper also provides details of the care expected of nurses for individual diseases. For example, for asthma, nurses are expected to diagnose, use and interpret peak expiratory flow meter readings, treat acute exacerbations and understand the treatment of chronic asthma. They are required to understand the aetiology and nature of asthma, educate the patient and family, understand the risk factors associated with increased morbidity and mortality of asthma, and to know when to refer patients for further acute or chronic care.

For tuberculosis, nurses are expected to know how to recognise and investigate tuberculosis suspects, and to initiate, follow-up and treat those shown to have tuberculosis on further investigation. They are also expected to adhere to the diagnostic and management protocols, and to complete the tuberculosis register for monitoring and evaluation purposes.[26] They must also know when to refer ill patients to hospital, and/or social services, and what the side effects of anti-tuberculosis medications are.[26] Contacts of tuberculosis patients are to be screened for tuberculosis and the patient, relatives and community appropriately educated. Voluntary Counselling and Testing (VCT) should be offered to all patients and the nurse must know how to provide education to patients about HIV and AIDS and sexually transmitted infections.

By 1996, 86% of nurses were employed in the public sector, but only a minority was in primary care,[30] and many were inequitably distributed throughout the health care system.[31] Currently, there are more nurses per 100 000 population than doctors (33.2 vs 2.5 full time equivalents per 100 000),[32] with many working in primary care. Yet, about sixty percent of primary care facilities have no nurses with primary health care training qualifications.[33] In a survey conducted in 2003, the percentage of nurses trained in HIV/AIDS, tuberculosis diagnosis and management, and prevention of

mother to child transmission of HIV over a 12-month period was shown to be 30%, 29%, and 27%, respectively,[31]

2.5 Primary care facilities

By 2003, 35% of existing primary health care facilities were built,[31] and with most (1345 clinics) having been built between 1994 and 2004.[34] According to data from the National Primary Care Facilities Survey,[35] a typical facility is managed by a nurse with a professional nursing qualification degree or higher. It is open for 5 days a week, for about 9 hours. Only one third of facilities offer 24 hour services, and staff turnover is high.[31] A typical rural clinic is staffed by 2 to 3 professional nurses, 2 to 3 enrolled nurses, and 1 or 2 nursing assistants.[36] Although equipment is available in most clinics, key items such as thermometers, stethoscopes, baumanometers, and otoscopes are not plentiful (Table 1). Most (96%) facilities are stocked with the most commonly used medications, but fewer than 10% have regular full supplies of all 25 essential drugs.[31] The EDL and STG are available in almost all clinics. Table 1 lists the services provided to or by primary health care facilities in South Africa.

Table 1: Services provided to or by primary health care facilities in South Africa.

Indicator (2003)§	
Availability of ambulance during working hours*	94%
Availability of ambulance after working hours*	72%
Expected time for ambulance to arrive at facility (travel time plus 20 minutes)*	54 minutes
Actual time for ambulance to arrive at facility*	113 minutes
Clinics providing the following primary care services:**	
Immunisation	67%
Family planning	88%
Antenatal care	55%
Sexually transmitted infection	94%
Tuberculosis	89%
Prevention of mother-to-child treatment	20%
Voluntary counselling and testing for HIV	70%
Clinics with access to laboratory services***	
HIV rapid test on-site	47%
HIV (ELISA)	70%
Syphilis	92%
CD4 count	22%
Pap smear	64%
Sputum microscopy for tuberculosis	93%
AFB turnaround time***	5.5 days
Availability of the following equipment:****	
Stethoscope	96%
Otoscope	88%
Oxygen cylinder	77%
Availability of the following equipment in the consultation room:*****	
Stethoscope	85%
Otoscope	21%
Thermometer, stethoscope, baumanometer, and otoscope)	7%

§ Taken from: The National Primary Health Care Facilities Survey
*: Page 19
**: Pages 9-14
***: Page 18
****: Page 25
*****: Page 26

2.6 Barriers to delivery of comprehensive primary health care by nurses in South Africa

Skills and knowledge of nurses. Studies on the knowledge and skills of primary care nurses working in South Africa indicate, that nurses are not necessarily competent to provide quality primary health care.[37 38 39 40 41 42] In-service training curriculae have and are being changed. But these changes do not appear to have affected the majority of nurses who have already qualified. The decentralisation of nurses from secondary and tertiary care to primary care, the integration of previously verticalised programmes into an integrated comprehensive primary care package, and the predominantly hospital-based training of most qualified nurses have resulted in a primary care workforce that is not fully equipped to provide a wide-range of basic primary health care services. The National Primary Health Care Facilities Survey[35] concluded that 90% of nurses knew how to treat tuberculosis, 89% of nurses knew how to prepare oral rehydration solution, 88% knew how to treat urethral discharge, and 69% were able to correctly treat genital ulcers. There was however a wide variation in the knowledge of nurses between the provinces. For example, nurses in the Free State (72%) and Western Cape (73%) performed worst at prescribing treatment for tuberculosis, and this possibly reflects the verticalisation of these programmes in these provinces.

Lack of standardised diagnostic, management and referral protocols. A lack of clinical management protocols has been cited as another barrier to the provision of comprehensive health care by nurses,[43] yet a large number of guidelines and protocols can be found in most primary care facilities in South Africa.[35] The EDL and STG are said to "have the potential to be powerful tools for the improvement of clinic nursing services if the knowledge base and scope of practice of nurses is recognised".[27] But failure to train nurses in their use was said to be a major factor impeding the implementation of the first EDL edition, as no formal strategy for dissemination and implementation appeared to be in place.[44] A study evaluating barriers to the application of diabetes guidelines in primary care suggested that time constraints, conflict of guideline recommendations with local practices, and health system

problems were common factors influencing their use.[45] This confirmed findings of other studies evaluating the care of diabetes mellitus by nurses and doctors in primary care in South Africa.[46 47]

Clinic factors. There is a pressing need for more nurses. The availability of professional nurses in the public sector declined between 2000 and 2002 but increased slightly between 2002 and 2003.[34] Factors resulting in a shortage of primary care nurses are said to be an increase in the number of patients accessing care in response to the free health care policy for children and pregnant women, an increase in the number of new or upgraded clinics, loss of nurses to other countries or the private sector, a lag in the number of nurses trained, and the HIV/AIDS epidemic that is not only placing excessive pressure on nurses and causing them to resign, but also resulting in their deaths.[48 49] Increased workloads also prevent many nurses from being available for training. Inadequate resources and below standard facilities have been reported to prevent nurses from applying their skills because of absence of necessary equipment. These deficiencies have also been said to increase their personal stress as it emphasises their own lack of skills in managing patients in resource-poor settings.[50] Ijumba highlights how the high administrative load and external district or provincial 'demands' impact their ability to plan,[51] and the negative effects of limited managerial supervision.

Drug policy. Section 38A of the Nursing Act[52] defines the schedules and conditions under which nurses may prescribe medicines. However, confusion about which qualifications a nurse requires in order obtaining a prescribing permit, and failure of the EDL to be explicit about exactly which medications nurses can prescribe have been cited as real and perceived barriers to care.[53]

2.7 Summary

The role of the nurse has evolved over the past 15 years in line with the changes in health policy in South Africa towards the goals of Alma Ata. They now play a central and defined role in primary health care delivery. However, their numbers and training have lagged behind, and are resulting in serious problems in service delivery. Strategies to relieve these problems have been devised, but much more needs to be done. There is a need for fresh approaches to equipping and training nurses in primary care to perform their duties more efficiently. The PALSA approach has potential in this regard.

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Chapter 3 : LITERATURE REVIEW: Origins and evolution of evidence-based and syndromic guideline development methods

3.1 Introduction

Literature, in the form of text books, treatment recommendations, immunisation schedules and algorithms have been used for many years to guide health care practitioners.[1] But over the last 20 years this literature mainly in the form of clinical practice guidelines has evolved and has increasingly focused on providing diagnostic and management recommendations that are explicitly linked to evidence. These evidence-based guidelines have mostly been developed in and for developed countries according to rigorous methodologies. In parallel with, but not in isolation of this process, several international bodies began to consider developing guidelines for resource-poor settings, many of them symptom and sign based.

In this chapter the origins of evidence-based guidelines, the evolution of methods used to develop them, and pertinent issues relating to their implementation and use in clinical practice will be briefly overviewed. Thereafter, the origins of integrated, syndromic guidelines, and the first guideline-based programme of its kind will be presented.

3.2 EVIDENCE-BASED GUIDELINES

3.2.1 The origins of evidence-based clinical practice guidelines

Clinical practice guidelines originated in the late 1980's, and their use gained prominence with federal agencies, medical speciality societies, health care funders, legal agencies, and other interest groups.[2] At the time, the major reasons for the increased awareness of the need for clinical guidelines were rising health care costs,[2] wide geographic variations in the way physicians' delivered health care,[3 4 5 6 7] and evidence of increasing clinical uncertainty amongst health care professionals.[8] Other

influencing factors were a rise in the use of unnecessary investigations, and escalating provision of inappropriate treatments to patients.[9]

3.2.2 The definition of clinical practice guidelines

Clinical practice guidelines are defined as "systematically developed statements to assist practitioners and consumer decisions about appropriate health care for specific clinical circumstances".[10] They have also been described as being decision-making tools intended to minimise disparities between current and best possible practice.[11] Evidence-based guidelines, on the other hand, are defined as clinical practice guidelines that have been developed after retrieval and appraisal of the medical literature using specified and systematic methods. The evidence included in these guidelines are described in terms of its strength, and recommendations are graded and linked to the appraised evidence. They are generally considered to be superior to those developed using other methodologies.[12 13 14]

Systematic reviews have shown that guidelines can improve clinical practice,[15] as well as patient outcomes.[16] They are also said to standardise diagnostic processes and management of patients, and reduce practice variations by closing the gap between what scientific evidence supports and what clinicians do.[17] In settings where resources (money, human and physical) are limited, they can improve the efficiency of health care services through standardisation of care.[17] Additionally, they also serve as educational tools,[18] and can influence public policy by highlighting priority health problems, areas of poor service delivery, and neglected or high risk patients not previously recognised.[17]

3.2.3 The evolution of evidence-based guideline development

3.2.3.1 Consensus-based guideline development

Initially, the only methods used to develop guidelines were consensus-based, and the quality of the evidence supporting the guideline recommendations was not always considered.[19] Recommendations were made on the basis of consensus achieved after open discussion, and the process of decision-making relied on the pooled knowledge and collective experience of the experts. This method is often referred to as *global subjective judgment.*[20]

In the late 1970s, more formal ways of gaining consensus were introduced. In the first method, known as the *consensus conference*, a clinical question was discussed by a panel.[21] [22] A group of experts were selected and requested to present the latest evidence and practices to the panel and other interested parties, including representatives from the public at a 2 or 3 day conference. The panel then met behind 'closed doors' to formulate recommendations based on the presented information. On the final day, the recommendations were made public. Major criticisms of this technique are that it failed to make explicit how the presented evidence related to the final recommendations, and that too short a time was allocated for their development (usually one or two days).[23]

A second consensus-based development method, the *Delphi-technique* was introduced in the early 1980s,[19] [24] and was considered to be a more formal method of developing consensus. This method was initially developed in the 1950s for other non-health related purposes.[25] The methodological steps are as follows. After selection of a topic (usually a medical or surgical procedure), the medical literature was reviewed. A panel then reviewed the evidence, for example, how appropriate a procedure was for a particular indication and allocated a score. These recommendations were then circulated to other clinicians who also scored these recommendations. The scores were made available to the panel and were discussed, particularly those

recommendations about which disagreement existed. After discussion, the scoring process was repeated and the final ratings (which reflected the degree of disagreement between the experts) were used to generate final recommendations. A variation of this method used questionnaires to record the views of clinicians on the topic under discussion.[25] A panel reviewed the questionnaire responses and this process was repeated until the final recommendations were made. The strengths of this method are that it gathers the opinion of a wide range of specialists and is relatively easy to implement. A disadvantage is that it is largely based on opinion with little indication of how scientific literature influences the development of the recommendations. Because the methods underpinning the Delphi techique are not made explicit it is not easy to assess how consensus is reached.[20]

The final method is known as the *Nominal Group Technique (NGT)*,[26 27] or the *'modified-Delphi method'*. This technique is also considered to be a form of formal consensus guideline development.[25] After a topic is identified, each participant records his thoughts. These are then presented in a round-robin fashion to a facilitator who records them. Each opinion or idea is discussed, and each member ranks them in terms of importance. The ranking is recorded 'anonymously' and presented to the facilitator who records each member's ranking for each idea. These rankings are tallied, and those with the highest scores are considered to be the final recommendations. The advantages of this method are that it encourages discussion around each topic and explores each idea or opinion individually. Disadvantages are that because of the heavy reliance on decision-making, it is very hard to determine the influence of evidence on the final recommendations. A modified version of the NGT, the modified-Delphi method, relies on the responses of mailed questionnaires to generate ideas. The respondents are invited to attend a session such as the one described above in order to determine the final recommendations. [25]

3.2.3.2 Evidence-based guideline development

In 1979, the Canadian Task Force on the Periodic Health Examination[28] introduced the practice of quantitatively assessing the quality of scientific evidence, and proposed that guideline recommendations be linked to their supporting evidence.[28] This was one of the first major moves to developing evidence-based guidelines. After extensive and systematic review of the literature, each retrieved study is coded according to the quality of its evidence as determined by its study design. Based on the retrieved evidence, recommendations are derived. The final recommendations are then graded to reflect the quality of the supporting evidence. The limitations of such a rigorous approach however is that scientific evidence for the effectiveness of the diagnostic and treatment recommendations are often lacking, or are of poor quality.[19] Therefore evidence-based guideline methods combining this approach with consensus-based methods were introduced.[19 29 30] Table 2 outlines the grading system introduced by the Canadian Task Force on the Periodic Health Examination.

Table 2: An adaptation of the Canadian Task Force Classification of Recommendations and Study Designs*

Category	Description
	Study designs**
I	Evidence obtained from at least 1 properly designed randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomisation.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
II-3	Evidence obtained from comparisons between times or places with or without intervention; dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.
III	Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.
	Recommendations
A	There is good evidence to support the recommendation that the condition be specifically considered in the periodic health examination.
B	There is fair evidence to support the recommendation that the condition be specifically considered in the periodic health.
C	There is poor evidence regarding the inclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.
D	There is fair evidence to support the recommendations that the condition be excluded from consideration on the periodic health examination.
E	There is good evidence to support the recommendation that the condition be excluded from consideration in the periodic health examination.

* Source: Woolf et al[2]

** Prior to 1984, category II-1 was not included in the scoring table.

3.2.4 Methods of evidence-based guideline development

Methods of guideline development according to rigorous methodologies are promoted by many specialty societies and guideline development agencies in North America,[31] Europe,[32 33] and New Zealand.[34] A review of guideline development methodologies used by these organisations shows little deviation from those originally published in the early 1990s.[19 35] The following five methodological steps common to all are[19 36]: (1) identification of topic and refining of the subject area (2) formation, convening and running of a development group (3) retrieval and assessment of clinical evidence (4) derivation and grading of treatment recommendations, and (5) external review of the guideline.

Topic identification and refinement of subject area. The first step of evidence-based guideline development involves identifying a guideline topic (condition, presenting complaint, procedure), and determining whether the guideline will focus on disease prevention, diagnosis, or treatment. The guideline development group then refines the subject area by determining the level of care (primary, secondary, tertiary) at which the guideline will be targeted, and who the end-users will be.

Formation of the guideline development group. The composition of the guideline development group is a major determinant of the guideline's validity.[35] The group should be multidisciplinary in nature to ensure a wide range of views and reduce bias in the final recommendations.[35 37] An ideal group consists of between 6 and 15 members, and each member's role should be clearly defined. The group leader should preferably possess clinical and group process skills,[38] but does not necessarily have to be an expert in the field.

Retrieval and assessment of evidence. Members of the development group then conduct a systematic review of the medical literature using search strategies that are conducted according to specified inclusion and exclusion criteria.[39] Information on the benefits, harms, and costs are extracted from relevant studies.[35] The internal validity ("the extent to which the study provides valid information about the type of conditions

represented in the study"), and the external validity ("the generalisability of the results to conditions outside of the study setting") are assessed. [35] Primary research is when the group conducts its own appraisal of the existing evidence and assesses its quality, whereas secondary research uses existing systematic reviews.[36] The latter may be necessary when time or resources limit the undertaking of new research. The strength of evidence-based guidelines are said to lie in the next phase, which is when the evidence is categorised according to its susceptibility to bias by using schemes similar to that presented in Table 2. Several strength of recommendations schemes exist.[40 41]

Derivation and grading of treatment recommendations. The categorised evidence is made available to the guideline development group who interprets and assesses it for relevance to the context in which the guideline will be implemented (clinical, public health, policy, or government).[35] In particular, the generalisability of evidence to the population in which the guideline is to be implemented is considered. The aim of this process is to derive recommendations based on the opinion of the guideline development group. After discussion, the derived recommendations are graded according to the groups' confidence that the health outcomes presented in the guideline will be achieved if adhere to. It is also during this process that formal consensus development methods as discussed above are commonly used to develop and grade the recommendations.

External review of the guideline. The complete guideline is then sent out for review by respected professionals in the field of interest.[35] Those consulted should represent a wide range of opinions and spheres of practice, but should definitely include a majority from the area of clinical practice (representatives) for which the guideline is intended. The comments of reviewers are considered and where considered relevant, are included in the report. Future revision of the guideline is essential, and this is prompted by ongoing systematic review of the medical literature.

3.2.4.1 Local adaptation of clinical practice guidelines

Adaptation (tailoring) of existing clinical guidelines to local practices, resources, and barriers to the delivery of effective health care has been shown to be one of the most effective strategies to ensure acceptability and use of guidelines.[42 43 44 45] Other advantages are that this process facilitates more effective implementation,[46 47] and increases the use of protocols[62] as has been shown by the Scottish Intercollegiate Guidelines Network (SIGN) group.[44] Before deciding to locally adapt national guidelines general characteristics such as its generalisability to the local population and setting, and its feasibility in terms of local organisational and financial resources should be considered. The adaptation process should include relevant roleplayers (respected experts and other individuals), the intended target users, and sometimes patients.[62] Local adaptation is said to increase ownership of the guidelines, local innovation, and to engender change in clinical practice.[62 48 49 50]

An important potential disadvantage of local adaptation is that it may reduce the validity of the guideline's recommendations, thereby impeding the attainment of its intended outcomes.[51] This is of particular consideration if the setting in which the guideline is to be implemented is different to the one for which the source guideline was originally intended. No formal framework for assessing the impact of the local adaptation process on the validity of the guideline's recommendation exists.[52] Up until 2006, no validated process for adaptation of guidelines developed in one setting for use in another had been proposed.

This has led a group of researchers, the ADAPTE group, to very recently propose a framework for local adaptation (trans-contextual adaptation) of guidelines.[52] An outline of the framework mirrors the methods used to develop evidence-based guidelines and is as follows.[52] The first step of guideline adaptation is the same as that for guideline development (identification of topic and context). Step two involves a search of guideline resource databases, and websites of guideline development agencies and other search engines. Step three is to assess the content of the source guidelines and compare the clinical questions with those questions defined by the

guideline adaptation group. The next step is to evaluate the quality of the guideline (AGREE instrument[53]), and to appraise how current, applicable, and acceptable the evidence is. Finally, the recommendations are adapted to local conditions and the guideline is externally reviewed, and adopted, endorsed and implemented. The group states that within the next few years, they wish to further advance knowledge regarding how to best adapt guidelines for local settings, and how to evaluate the validity of these guidelines.

3.2.4.2 What makes guidelines work?

Developing an evidence-based guideline does not guarantee its use in clinical practice. Grimshaw et al[54] reviewed 44 systematic reviews on strategies aimed at changing medical practitioners' behaviours and reported that passive dissemination of guidelines (for example, posting them to practitioners) may be useful at increasing physician awareness of the need to change clinical behaviour, but is unlikely to effect such a change. By contrast, active implementation which involves the intentional introduction of the guideline into clinical practice using a number of strategies, rather than merely posting it or assuming that the practitioner will make an effort to retrieve and refer to it, is shown to be more effective. However, a second review of 235 studies published 5 years later concluded that it remains uncertain which guideline implementation strategy or combination of strategies is most effective.[55] A list of the implementation strategies reviewed in that study is presented in Table 3.

Table 3: List of potential intervention used to implement guidelines*

Intervention
Education materials
Educational meetings
Consensus processes
Opinion leaders
Patient-directed interventions
Audit and feedback
Reminders
Other professional strategies (including mass media and marketing)
Financial incentives
Organisational interventions
Structural interventions
Regulatory interventions
Multifaceted interventions (a combination of different strategies)**

* Adapted from Grimshaw et al.[55]
** [56 57]

Factors preventing the use of guidelines by practitioners range from personal attitudes and personality traits to the guideline itself.[58] Professional barriers include factors relating to health professionals' knowledge of guidelines; and their lack of skills in locating, using or applying it to practice.[59] Environmental factors relate to whether or not colleagues, managers, or opinion leaders (social factors) support the guideline recommendations. Finally, economic considerations for the doctor, the patient and the health care system are other major barriers to their use by health care professionals.

3.2.4.3 Ensuring effective implementation

To ensure effective implementation, the following are required[60 61 62]:

- Knowledge of the target audience and current clinical practice.
- Knowledge of guideline development methods.
- Identification of barriers to change, and knowledge of gaps between current and ideal practice.
- A clear statement of key recommendations (messages) from the guideline.
- Knowledge of the effectiveness of the various dissemination and implementation strategies.
- Logistical support or information (a budget, development and implementation time frame).
- A plan to evaluate the implementation strategy.

Qualitative research (interviews, direct observation) plays an important role in guideline development and implementation, as it can provide information about perceived or actual barriers to the delivery of effective clinical practice by health care professionals. It also provides information on the best implementation strategy to use, gaps in clinical practice, and the acceptability of the proposed guideline and its implementation strategy. The use of qualitative evaluation as part of the design of an intervention strategy is of particular importance when designing a complex intervention (a multicomponent intervention targeting a health professional to ensure a change in professional behavior), such as the one presented in this thesis.[63]

3.2.5 Summary of evidence-based guideline development

Methods of guideline development have evolved over the past 20 years with a shift from primarily consensus-based development to those incorporating more rigorous appraisal of existing scientific literature combined with formal consensus. Despite the increased emphasis on evidence-based guideline development, evidence is lacking as

to what the most effective strategies to disseminate and implement these guidelines are. Local adaptation of existing guidelines and implementation strategies to address identified local barriers to change, however, is one approach that is said to promote their implementation and thereby their uptake and use in clinical practice.

3.3 INTEGRATED SYNDROMIC GUIDELINES

3.3.1 Origins of integrated syndromic guidelines

In parallel to the expansion of the evidence-based guideline development movement has been the emergence of integrated syndromic guideline-based programmes. Syndromic approaches to disease management have been used for many years. This approach was made prominent through the development of protocols for the management of sexually transmitted infections (STIs) whereby a genital discharge is treated empirically with a range of medications targeting a number of possible underlying aetiologies. STI guidelines however target one cluster of diseases.

Syndromes are defined as "a group of symptoms and signs that occur together and characterise a particular abnormality or condition"; integration means "to incorporate [parts] into a larger unit".[64] Together these definitions summarise what integrated syndromic guidelines do. They incorporate a number of related conditions into one document, and group them into disease syndromes according to the correlations between their symptoms and signs and the diagnosis (syndromic diagnoses), and/or according to their common responses to medications (syndromic management).[65 66] Syndromic, integrated guidelines are typically algorithm-based. Clinical algorithms are defined as being "written guide[s] to stepwise evaluation and management strategies that require observations to be made, decisions to be considered, and actions to be taken".[67] They have also been reported to accelerate learning, retention of information, and results in faster adherence to recommendations than information presented in text.[68 69 70]

For the purpose of this review, strategies based on the development of more comprehensive guidelines that integrate a larger number of conditions will be discussed. The shift to develop this type of guideline was made prominent by the World Health Organization's (WHO) Integrated Management of Childhood Illnesses (IMCI) initiative.[71] Other similar programmes are the Practical Approach to Lung Health (PAL) strategy,[72] the IMAI (Integrated Management of Adolescent and Adult Illnesses) programme,[73] and finally, the PALSA (Practical Approach to Lung Health in South Africa) initiative on which this thesis is based.

3.3.2 Integrated Management of Childhood Illness (IMCI)

The IMCI programme was introduced in the early-1990s.[71] It originated in response to a number of events. The first being the high mortality rate of children under the age of 5 years due to diarrhoea, pneumonia, and respiratory tract infections in developing countries. The second being the favourable outcomes of disease-specific and other health-related programmes (such as immunisation and Vitamin A supplementation) on reducing childhood mortality and strengthening health systems. A third factor was the failure of health care workers to recognise these conditions because of their common presentations.

The World Health Organisation's Child Health and Development (CHD) department, in collaboration with UNICEF (United Nations Children's Fund), therefore agreed to develop a guideline that integrated successful disease-specific programmes such as the WHOs programme for the Control of Diarrhoeal Disease and the Acute Respiratory Infections programme into one.[74] The 3 main components of the programme were[75]: (1) to develop a locally-adapted guideline on the integrated management of sick children in *Falciparum malaria* endemic countries with mortality rates of greater than 40 per 1000, thereby improving the case management skills of primary care health care workers (2) to through its activities, strengthen the health system, and (3) improve the care of children in and by the family and community. Case detection was to be based on simple clinical information, no laboratory features, and a response to empiric treatment. The clinical signs included in the guideline were to be easily recognisable by health care workers and sensitive in detecting disease.

The diagnostic information was presented as algorithms, and the steps included in the guideline included assessment, classification, treatment of the child, and counselling of the mother.

3.3.2.1 Development of the generic IMCI guideline[76]

The steps used to develop the generic guideline are as follows. After identification of the topic, the first step was to form a working group which collaborated with 12 WHO programmes and other experts or representatives from interested organisations. Thereafter, existing guidelines and treatment protocols of each related programme was informally appraised for its evidence-base and deficiencies. One example of the outcome of this process was the realisation that many programmes did not provide adequate outpatient counselling for mothers, and this was identified as a gap between current and optimal practice. After a number of meetings, the draft guidelines were integrated and refined, and were then circulated to experts for external review and comment. Based on the guideline, support materials were developed to be used during training. The training course was designed to combine classroom and clinical work. Concurrently, studies to validate the diagnostic and treatment recommendations were conducted to produce algorithms that were as accurate and simplified as possible.

3.3.2.2 Assessment of the validity of the generic IMCI guidelines

The accuracy of the diagnostic performance of the IMCI guideline, in other words its validity, was in doubt because of the paucity of evidence on the accuracy of symptoms and signs to diagnose conditions included in the guideline, and because of the manner in which it was developed.[76] This initiated a series of validation studies which served to test the accuracy of the guideline's algorithms by comparing certain aspects of it to the performance of experienced physicians with access to laboratory investigations and chest radiography.[75] A secondary outcome was to determine how the guideline could be improved. Studies in Gambia[77] and Kenya[78] were conducted to determine the accuracy of the symptoms and signs used in the guideline in assessing and classifying disease (Table 4). The next 4 studies were conducted to determine the

accuracy of the guideline after nurses underwent training in its use.[79 80 81 82] This served to inform the next guideline revision. A final study was then conducted using the revised materials.[83] Table 4 provides an overview of the most relevant early validation studies.

Table 4: Overview of the results of selected IMCI validation studies*

Study setting	Aim	Results	Results	
Weber et al[77]	To test IMCI	n=440		
The Gambia	diagnostic	Disease:	Sens (%)	Spec (%)
	algorithms in an	Pneumonia	81	89
	area with	Dehydration	67	96
	seasonal	Malaria parasitaemia (any level)	87	8
	malaria.	Malaria parasitaemia (high level)	100	9
		Measles	100	99
	Reference	Otitis media	31	97
	standard:	Malnutrition	89	90
	paediatrician			
Perkins et	To test IMCI	n=440		
al[78]	diagnostic	Disease/action:	Sens (%)	Spec (%)
Kenya	algorithm in a	Pneumonia	97	49
	high malaria	Dehydration with diarrhoea	51	98
	transmission	Malaria	100	0
	area.	Ear problem	98	2
		Nutritional status	96	66
	Reference	Appropriate referral	42	94
	standard:	Fever recognition	91	77
	paediatrician			
Simoes et	To test a trained	n=449		
al[79]	PHC* worker	Disease:	Sens (%)	Spec (%)
Ethiopia	using IMCI	Pneumonia	88	87
	algorithms.	Diarrhoea with dehydration	76	98
		Malnutrition	85	96
	Reference	Malaria	39	99
	standard:			
	paediatrician			
Kolstad et	To test the	n=1226		
al[84]	performance of	Disease:	Sens (%)	Spec (%)
Uganda	IMCI diagnostic	Severe pneumonia	53	93
	algorithms	Pneumonia	76	60
		Diarrhoea	91	88
	Reference	Dehydration	25	99
	standard:	Severe malnutrition and severe	19	97
	medical officers	anaemia		

* PHC – primary health care; Sens: sensitivity; spec: specificity.

3.3.2.2 Implementation of the generic IMCI guidelines

Implementation of the IMCI strategy comprises three phases.[85] In the first phase (introduction), the strategy is presented to key Ministry of Health and other government officials and interested parties with the intention of fostering an interest in the programme. If the strategy is agreed to, the second, or early implementation phase, is initiated. The Ministry of Health then starts plans for implementation and monitoring. It is in this phase that adaptation of the generic guideline to match local epidemiological patterns, health systems structure, processes, and cultural patterns is started. Policies, drug availability, health information systems, and communities are reviewed and engaged if needed. In the final phase (expansion), the intervention is rolled out to other districts; and the programme is evaluated by measuring outcome indicators. By 2004, the programme had been implemented in most African, South American, and Asian countries.[86]

An evaluation of the programme in 5 countries has shown that IMCI improves health worker assessment, diagnosis and treatment of childhood disease, and results in early and appropriate management.[87] It is associated with lower costs per child treated, and improves global public health views and practices regarding child health. Barriers to the effective implementation of the programme are poor supervision, increased staff turnover, slow uptake of the programme, and low morale amongst health workers.[88] The IMCI programme has subsequently expanded and now includes guidelines targeting households, communities, and referral facilities.[87]

3.3.2.3 Local adaptation of the generic IMCI guideline

Steps in the IMCI adaptation process are detailed in a comprehensive document.[89] These are (1) to initiate the adaptation process (2) to review current clinical guidelines and policies (3) to outline the adaptation process, and start a preliminary plan (4) to set up and facilitate meetings with the adaptation subgroup (5) to adapt the clinical guidelines (6) to circulate the guideline for comment and review. This process relies heavily on relatively informal consensus development methods but materials and checklists have been developed to ensure that the parts of the guideline and materials

that are adapted are standardised between the countries. In addition, the adaptation document lists which sections of the guideline are to be adapted. These relate to first-line antibiotics, choice of complimentary foods, and the use of local terms for symptoms and signs included in the guideline. Other adaptations are dependent on the local prevalence of HIV and malaria, and on local policies pertaining to Vitamin A supplementation.

3.3.3 Integrated, syndromic guideline-based programmes modelled on the IMCI strategy

Following the successful development and implementation of the IMCI programme, the WHO Stop-TB strategy commenced the development of the PAL strategy.[§] This programme, as discussed in Chapter 1, was introduced to improve the case detection of tuberculosis, and also to improve the recognition and management of other respiratory illnesses in primary care in resource-poor countries. It was intended to provide a continuum of care by providing case management skills to health care workers for the recognition of disease in adolescents and adults who were already familiar with the IMCI programme.[90 91] Development methods were the same as that for IMCI, and a number of documents detailing the outcomes of meetings held are available.[92 93 94 95 96 97] However, explicit details of the development processes have not been published. One of the strengths of the generic PAL guideline is that systematic reviews on the treatment recommendations included in the guideline were conducted.[98 99 100] The IMAI programme is an expansion of the PAL strategy and addresses the management of other priority adolescent and adults diseases (diabetes, cardiovascular conditions, and HIV and AIDS), and is also currently being implemented in a number of countries.[73]

[§] PAL was previously known as the Adult Lung Health Initiative (ALHI)

3.4 Adoption of evidence-based guideline development methods by WHO

In 2003, WHO published a document detailing methods to be used for the development of WHO guidelines.[101] This marked a shift from the use of primarily consensus-based development methods to the adoption of more evidence-based ones. It is suggested that WHO guidelines in general are to consider the most efficacious, cost-effective, affordable, and beneficial recommendations for populations as opposed to individuals with disease. The latter, addressing population rather than individual needs, is cited as one of the main differences between evidence-based guidelines and those guidelines developed by WHO. When comparing the methods proposed in the document to those used by the IMCI and PAL guideline developers there are many similarities, except that in the WHO document a strong emphasis is placed on ensuring that systematic reviews are conducted; that the derived recommendations are linked to evidence; and that the implications of these recommendations on costs and the health of the population be made explicit. It was recommended that the latter be done through use of a number of scenarios. The reason for the provision of a number of scenarios are to ensure that countries with limited resources are able to choose the best recommendations from amongst a number of possible recommendations given their local circumstances.

3.5 The recent development of integrated, syndromic guidelines in developed countries

Over the past two years, algorithmic integrated guidelines have been developed by medical societies in North America[102] and Europe.[103] They have been developed to assist busy practitioners in general practice who have limited access to, or use of, diagnostic technology. They are both syndromic in that they are not disease-specific and do not require a precise diagnosis.

The first, developed by the ACCP[102] (American College of Chest Physicians) provides an empiric integrative approach to the patient with unexplained cough. Although there is extensive literature on assessing the causes of unexplained cough, the decision to develop an empiric approach stems from the fact that the most common causes of cough are attributable to a limited number of conditions, and that use of simple treatment algorithms avoids the need for expensive confirmatory tests.[104 105 106 107 108 109] This empiric approach also results in high levels of treatment success. The algorithms provide approaches for acute, subacute, and chronic coughs, and all recommendations are graded.[104]

The second integrated guideline developed by the International Primary Care Respiratory Group (IPCRG) uses a syndromic approach to the diagnosis of common chronic respiratory diseases.[110 103 111] Cough, wheeze, chest tightness, breathlessness or chest pain are entry points into the guideline. Its four main diagnostic algorithms address the diagnosis and management of conditions according to 3 age groups (children, adults, and older people). Clinical information, based on validated questionnaires classifies patients into the most likely disease syndrome. Supporting papers are provided,[112 113 114] and the evidence is graded according to a ranking system. A document proposing a course of action for its dissemination and implementation was also produced.[115] It was suggested by one of the authors that such a symptom-based approach to chronic respiratory diseases in developing countries is needed.[103]

3.6 Summary

Based on the literature reviewed in this chapter it appears that the two 'parallel' models of guideline development seem to be merging. Pioneers of integrated syndromic guideline development are adopting more rigorous development methodologies, whereas some evidence-based guideline developers have recognised the need to develop guidelines that take into account the overlap of symptoms and signs of numerous diseases, and the limitations of assuming that the guideline users know the diagnosis of the condition with which the patient is presenting.

A locally-adapted syndromic approach integrating all priority respiratory diseases in South Africa is required. Therefore, in adapting the PAL guideline for South Africa, the development team set out as its goal to combine these methodologies as best as possible, given the local circumstances.

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Chapter 4 : LITERATURE REVIEW: Diagnostic accuracy of symptoms and signs that predict respiratory disease

4.1 Overview of the chapter

This review evaluates studies of the accuracy and precision of history and clinical examination as methods for diagnosing obstructive airways disease.

4.2 The role of clinical history and examination in diagnosing respiratory disease

History and physical examination have been said to provide most of the clinical information required to make a diagnosis.[1 2 3] Sackett[1] likened each component of the clinical examination (history findings, symptoms and signs) to laboratory tests in that their accuracy and precision can be quantified.[4] The accuracy of a test refers to the degree of agreement between the test and the gold standard against which it is assessed. It is quantified by measuring its sensitivity, specificity, likelihood or diagnostic odds ratios, and the area under the receiver operating characteristics curve (ARUC).[5 6] A test's precision refers to the probability that a particular clinical finding will be present in a patient with the target disorder under discussion. But unlike laboratory tests, little emphasis has been placed on determining the accuracy and precision of each component of the clinical history and examination to determine the disease under question.[1 4] This finding is supported by the absence of rigorous studies assessing the diagnostic accuracy of symptoms and signs to detect most respiratory conditions.[6]

Some of the earliest work done to evaluate the value of the clinical examination was undertaken in the field of respiratory medicine. A systematic review of 21 textbooks and 29 articles yielded 40 and 32 different signs predicting COPD, respectively.[6] None of these textbooks reported on the precision and accuracy of the signs, and only one of the studies was assessed as being methodologically robust.[7] A series which was

first published in The Journal of the American Medical Association (JAMA) in 1992, called The Rational Clinical Examination was initiated to publish systematic reviews to identify history and examination findings that are useful in clinical practice. It also aimed to identify gaps in existing literature.[1] However, only 50% of the reviews originally commissioned were completed[6] because of unavailability or low quality of supporting scientific evidence.[8] Of note was the absence of studies comparing findings made by a blinded independent observer to a 'blinded' reference standard amongst a large representative population of consecutive patients.[6] This study design is considered to be the best way to assess the accuracy of a test.[4] Reasons cited by the authors for the paucity of such studies are that they are usually difficult to design and conduct, particularly in primary care settings; that many investigators do not have the necessary statistical skills, for example, to do multivariable regression analysis; and that clinically the emphasis has shifted from skillful clinical examination to over-reliance on investigations. Other reasons are that this kind of diagnostic research is generally not considered to be a priority, given the increased emphasis on more sophisticated investigations. Clearly the latter trend brings with it increasing costs, placing such tests beyond the reach of much of the world.

4.2.1 Recognising respiratory disease

Early and accurate identification of respiratory illnesses has important implications for treatment and prognosis. For example, in asthma, inhaled corticosteroids reduce the number of symptoms and exacerbations and increases patients' quality of life.[9] For COPD, early recognition also improves patients' quality of life;[10] and the early institution of secondary preventive measures such as smoking cessation has been shown to reduce FEV1 decline over time.[11 12] The prompt diagnosis and treatment of smear-positive tuberculosis reduces the number of infectious cases in the community.[13] And the early introduction of appropriate antibiotics in community-acquired pneumonia is associated with improved prognosis.[14] On the other hand, viral upper respiratory tract infections require only symptomatic treatment. Thus, distinguishing between these categories is important.

In the PALSA guideline, knowing the accuracy and precision of common respiratory conditions diagnosed on the basis of history and examination is important. This is particularly relevant for the diagnosis of conditions characterised by airflow limitation, as diagnostic equipment such as spirometers are not available in primary care in South Africa. The rest of this chapter therefore presents the findings of a review of the literature focusing on the identification of individual or combinations of history and examination elements that assist with the diagnosis of obstructive lung disease, asthma, and COPD.

4.3 OBSTRUCTIVE AIRWAYS DISEASE

4.3.1 Identification of obstructive airways disease among patients with cough

As part of a prevalence study, **Thiadens et al**[15] examined 192 patients (18-75 years old) not known to have asthma or COPD who presented to primary care in the Netherlands with a cough for at least two weeks' duration. The aim was to determine whether asthma and COPD could be diagnosed on the basis of history and physical examination alone. The reference standards used to diagnose asthma or COPD in this study are presented in Table 5. Subjects completed a modified Medical Research Council questionnaire, which contained questions relating to respiratory symptoms, at baseline and at 8 weeks.

On univariable analysis of the presenting symptoms, an asthma attack in the past two weeks had the highest odds (odd ratio (OR) 7.2; 95% CI: 2.5-22.1), followed by breathlessness (defined as attacks thereof, being woken by it, or persistent symptoms) during the past two weeks (OR 4.2; 95% CI: 2.1-7.7), prolonged expiration* (OR 4.1; 95% CI: 1.7-9.4), and wheeze (OR 3.5; 95% CI: 2.0-6.6). Of the items of past medical history, worsening of symptoms after exposure to specific allergens such as dust, hay, moulds, and animals were the highest predictors (OR 5.0; 95% CI: 1.9-13.7). Others were: symptoms provoked by non-specific stimuli such as pollutants, exercise, cold

* Prolonged expiration on clinical examination was not defined in this study.

air (OR 3.7; 95% CI: 1.4-9.8), episodes of dyspnoea (OR 3.4; 95% CI: 1.7-6.7) and wheeze in past year (OR 2.9; 95% CI: 1.5-4.9). Symptoms not found to have significant odds were nocturnal cough over the past two weeks (OR 4.1; 95% CI: 0.7-2.5), atopy in childhood (OR 1.1; 95% CI: 0.5-2.6), family history of asthma (OR 1.0; 95% CI: 0.8-2.8), and nocturnal cough in the past year (OR 0.8; 95% CI: 0.4-1.6).

Logistic regression analysis confirmed that the most significant multivariable predictors of obstructive airways disease were[§]: reported wheezing (p=0.02), reported breathlessness (p=0.01), symptoms provoked by allergens (p=0.02), prolonged expiration on examination (p=0.01), female sex (p=0.02), and pack years of smoking (p=0.01) (Table 5). Using these variables, a scoring system was derived with the highest accuracy for diagnosing asthma or COPD yielding at a cut-off value of 3 (Table 5). At this value the PPV was 84%, and the NPV was 72% (76% of patients were correctly identified). Wheezing was a strong predictor of obstructive airways diseases, but a combination of variables, as opposed to a single variable, was shown to be most predictive. Of note, those individual items strongly predictive of obstructive airways disease (on univariable analysis) were not included in the logistic regression model, most likely due to their relationship with other variables (covariates).

Reported limitations of this study were that the scoring system was not validated in another population to determine its generalisability; and that the small number of patients in the study with COPD precluded determination of variables that predicted either asthma or COPD. The reference standards were reasonably robust, except that patients with controlled asthma may not have been included. the scoring system is however easy to use clinically.

[§] Odds ratios for predictors arrived from multivariable predictors not provided.

Table 5 Summary of findings for studies assessing history and clinical examination variables as predictors of obstructive airways disease.

Source and study design	Inclusion/exclusion criteria	Reference standard	Results
Thiadens et al[16] **Netherlands** **1998** Prospective (descriptive). Primary care practice.	Inclusion: • Ages - 18-75 • Cough ≥2 weeks Exclusion: • Asthma • COPD • CVS • Pulmonary disease Pregnancy.	For asthma: • In the last year 1 episode of wheeze, cough, dyspnoea for more than 3 weeks, *and* • PD_{20}≤15.6µmol methacholine *or* a positive bronchodilator response. For COPD: • If FEV1<70% of predicted at baseline and < 75% after 8 weeks, *and* • Reversibility <9% and FEV1 improvement <12%.	N=192 Females: 62%. Mean age: 44 years. Asthma-39% COPD-7% Cut-off of 3 indicates OAD. • Wheeze – 1 point • Attack of or nocturnal dyspnoea – 1 point • Prolonged expiration – 1 point • Pack years smoking – n/25 points • Symptoms provoked by allergies – 0.5 points • Female – 1 point
Badgett et al[18] **USA** **1994** Prospective (consecutive). Recruited by notices in hospital clinic.	Inclusion criteria: • ≥ 40, current/former smoker, *or* • Previous asthma, chronic bronchitis, or emphysema.	OAD: • FEV1<80% of predicted FEV1/FVC ratio <0.7.	N=92 (343 physician contacts) Female: 47%. Mean age: 56 years OAD: 35% Predictors of OAD: • Peak flow < 350L/min • Reduced breath sounds • ≥30 pack years
Van Schayck et al[17] **Netherlands** **2002** Cross-sectional. Random selection of patients visiting GP. Questionnaire (self-administered).	Inclusion: • 35-70 years • smokers • Not on respiratory medications.	Undiagnosed OAD: FEV1 < 80% of predicted	N=201 Female: 62% Mean age: 47 years FEV1<80%: 17% OAD if: 2 out of 3: • Chronic wheeze • Chronic cough • Chronic dyspnoea

4.3.2 Identification of patients with obstructive airways disease in high risk populations

To determine the performance of medical history, examination and peak flow measurements to identify obstructive airways disease (OAD) in high-risk patients (smokers; or those with self-reported diagnoses of asthma, chronic bronchitis, or emphysema), **Badgett et al**[18] recruited 92 patients from a university outpatient clinic. Patients 40 years and older who were current or former smokers, or had self-reported obstructive airways disease were assessed. Table 6 lists the significant individual predictors of OAD and the positive likelihood ratios calculated from their report for purposes of this review.

Logistic regression analysis identified 3 variables which significantly predicted the diagnosis of OAD. These were: peak flow measurements less than 350 L/min, reduced breath sounds, and $\geq$ 30 pack years of smoking (Table 5). The presence of any of these variables yielded a sensitivity of 98%, specificity of 46%, and an area under the ROC curve of 0.87. The authors reported that although self-reported diagnoses of asthma or COPD improved the performance of the model they were excluded from it to ensure generalisability to those without previous access to care. Reduced breath sounds predicted OAD better than wheezing.

Limitations of the study are that the model had not been validated in other populations, and that the studie's small sample size precluded defining predictors for each specified disease. The model is only applicable to populations aged 40 years and older.

Table 6: Statistically significant univariable predictors of OAD in patients ≥40 years at high risk of the disease (from Badgett et al[18]).

Univariable predictors	Sens (%)	Spec (%)	PPV (%)	NPV (%)	LR+ *
History variables					
Previous diagnosis of COPD (y/n)	59	78	59	78	2.7
Smoke (≥ 30 pack years)	63	67	50	77	1.9
Age (≥ 50 years)	88	40	44	88	1.5
Dyspnoea (Bathing, dressing or at rest (≥ 4))	47	78	54	78	2.1
Steroid use	31	92	63	71	3.9
Theophylline use	47	73	48	72	1.7
Previous diagnosis of asthma	35	83	52	71	2.1
Inhaler use	19	95	67	69	3.8
Home oxygen	13	97	67	67	4.3
Physical examination*					
Initial impression before examination only	41	81	54	71	2.2
Wheezes present	6	99	88	66	6
Reduced breath sounds	57	88	62	77	4.8
Mean FET# (≥ 4 seconds)	77	49	45	79	1.5
Final opinion after examination only	55	81	61	76	2.9

Sens: sensitivity; spec: specificity; PPV: positive predictive value; NPV: negative predictive value; LR: positive likelihood ratio.
* LR+ calculated for the purpose of this review.
# FET: Forced expiratory time.

Van Schayck et al[19] aimed to determine how well respiratory symptoms predicts airflow obstruction in current smokers; and whether selecting for age increases the probability of detecting smokers with airflow obstruction. Smokers aged 35-70 years (201 out of 651) were randomly selected from the databases of 2 semi-urban Dutch general practices. Eligible patients completed a questionnaire, and underwent spirometric testing. Undiagnosed OAD was determined if a FEV1 < 80% of predicted was detected. Eighteen percent of patients met these criteria.

The only variable significantly related to FEV1 < 80% was chronic cough (OR 2.50). A previous diagnosis of asthma or bronchitis, a history of allergies, tiredness, chronic dyspnoea and chronic wheeze were not found to be significantly related to airways obstruction. The combined odds for detecting OAD using 2 or 3 symptoms are shown in Table 7. The percentage of smokers with obstruction were shown to increase with increasing age. The chance of having bronchial obstruction also increased with age and was higher in those who coughed. The authors concluded that case finding by targeting smokers is a better option than screening all patients. Weaknesses of this study were the preponderance of females in the study population, and the limited sampling frame (two practices only).

Table 7: Predictors of OAD in smokers 35-70 years (from van Schayck19).

SYMPTOM	ODD RATIO (95% CI)	PPV	NPV
Family history			
• Asthma	1.03 (0.38-2.77)	18	-
• Allergy	1.35 (0.49-3.70)	21	-
Symptom			
• Tiredness	1.77 (0.77-4.06)	21	87
• Chronic wheeze	2.15 (0.94-4.88)	27	85
• Chronic dyspnoea	2.19 (0.98-4.90)	24	87
• Chronic cough	2.50 (1.14-5.52)	27	87
Number of symptoms(chronic cough, dyspnoea, or wheeze)			
• 1	2.28 (0.93-5.60)	22	89
• 2	3.02 (1.37-6.64)	29	88
• 3	3.01 (1.17-7.70)	35	85

* PPV-positive predictive value; NPV-negative predictive value.

In summary, these 3 studies, suggest that wheeze (reported or chronic), increasing pack years smoked, and dyspnoea (chronic, or attacks thereof, or occurring nocturnally) are predictive of obstructive lung disease (observed in two of the three studies) (Table 5). Cough is a predictor in only one study, but was part of the inclusion criteria in the third.[15] In one, female sex, symptoms provoked by allergies,

and prolonged expiration were also predictive and formed part of a derived scoring system.

4.3.3 Clinical examination features that predict the presence of airflow limitation

As part of the JAMA Rational Clinical Examination series, **Holleman and Simel**[20] pooled data from 21 studies to determine which clinical examination variables best predicted airflow limitation. Composite diagnostic characteristics of the history and examination findings of clinically robust studies were presented (Table 8). High cumulative pack year history had the strongest association with airflow limitation. Chronic bronchitis, chronic sputum production, and wheezing had a moderate association; and cough and dyspnoea had the weakest associations (Table 8).

Table 8: Findings taken from pooled data for 21 studies to determine the individual predictors of airflow limitations (from Holleman and Simel[20]).

History Item	PLR	NLR	Sens (%)	Spec (%)
Smoking history				
≥ 70 pack years vs <70 pack years	8.0	0.63	40	95
ever vs never	1.8	0.16	92	49
Sputum production ≥ ¼ cup	4.0	0.84	20	95
Symptoms of chronic bronchitis	3.0	0.78	30	90
Wheezing	3.8	0.66	51	84
Exertional dyspnoea				
grade 4 vs 3 or less	3.0	0.98	3	99
Any vs none	2.2	0.83	27	88
Coughing	1.8	0.69	51	71
Any dyspnoea	1.2	0.55	82	33
Examination Item	**PLR**	**NLR**	**Sens (%)**	**Spec (%)**
Wheezing	36	0.85	15	99.96
Barrel chest	10	0.90	10	99
Decreased cardiac dullness	10	0.88	13	99
Match test	7.1	0.43	61	91
Rhonchi	5.9	0.95	8	99
Hyperresonance	4.8	0.73	32	94
FET* (seconds)				
>9	4.8			
6-9	2.7	-	-	-
<6	0.45			
Sub-xiphoid cardiac apical pulse	4.6	0.94	8	98
Pulsus paradoxus	3.7	0.62	45	88
Reduced breath sounds	3.7	0.70	37	90
Accessory muscle use		0.70	24	100
Excavated supraclavicular fossae		0.69	31	100

PLR: positive likelihood ratio, NLR: negative likelihood ratio, sens: sensitivity, spec: specificity.
* FET: Forced expiratory time

Calculating likelihood ratios for the combinations of findings that best predicted airflow limitation revealed that no single or combination of symptoms or signs excluded airflow limitation (Table 9). However, a patient with a history of never having smoked cigarettes, and no history of wheezing, or wheezing on examination has a markedly decreased likelihood of having airflow limitation ((LR 0.18). In contrast, a patient with ≥70 pack year smoking history, decreased breath sounds, or previously diagnosed COPD has a high likelihood of having airflow limitation.

Table 9: Combinations of clinical examination items predicting airflow limitation taken from the pooled studies (from Holleman and Simel[20]).

CLINICAL EXAMINATION ITEMS TAKEN FROM RELEVANT STUDIES	RELATION TO AIRFLOW LIMITATION	REFERENCE STANDARD
Years of cigarettes exposure, patient-reported wheezing, objective wheezing.[21]	LR+ - varies LR- 0.18	FEV/FVC and FEV1<5th percentile
Patient-reported chronic obstructive pulmonary diseases, ≥ 70 pack-years of cigarette smoking, reduced breath sounds. • ≥ 2 findings present • < 2 findings present[22]	LR+ 34 LR- 0.34	FEV1 <60 5 of predicted or FEV1/FVC ratio <0.60
Dyspnoea, subjective wheezing, objective wheezing, accessory muscle use, excavation of supraclavicular fossae, and distension of external jugular veins.[23]	R= -0.64	
Breath sound intensity, use of scalene muscles, objective wheezing, and rales during coughing.[24]	Negatively correlated with FEV1.	FEV1
Decreased breath sounds, objective wheezing, rales, and prolonged expiratory time. • All 4 findings present • < 4 findings present[25]	LR+ 3.3 LR- 0.44	Abnormal FVC, FEV1, or maximal mid-expiratory flow.
History by questionnaire, standardized physical examination • Any abnormal finding • No abnormal findings[26]	LR+1.4 LR- 0.77	FEV1/FVC < 0.70

4.3.4 Differentiating between asthma and COPD

Beeh et al[27] also set out to identify items to distinguish between asthma and COPD. The aim was to find predictors that could be incorporated into a user-friendly questionnaire in clinical practice. Clinical data was retrieved on 546 patients from a specialist pulmonologist's database in Germany. The diagnostic criteria are presented in Table 10. Thirty eight percent had asthma and 62% had COPD. The following items were determined: age of onset of symptoms, smoking history, atopy, and productive or absent cough. Patient characteristics which were significantly different between asthma and COPD were age (33 years vs 55 years, $p < 0.0001$), age of onset (31 years vs 54 years, $p<0.0001$), male sex (43% vs 60%, $p=0.0008$), presence of atopy (75% vs 14%), current smoking (28% vs 68%, $p<0.0001$), and cumulative pack years (0 vs 30 years, $p<0.0001$). Asthmatics were more likely to have dry (65% vs 37%, $p<0.0001$) rather than productive (10% vs 45%, $p<0.0001$) cough.

Regression analysis of predictors for COPD showed that as the pack year number and age of onset increased, the likelihood as measured by odds ratios increased. In contrast, age of onset less than 20 years and never having smoked increased the likelihood of a diagnosis of asthma. Table 11 lists the derived scoring system. The scores range from 0 to 15, with a high score indicating COPD and a low score indicating asthma. The mean scores for COPD (10.5 ± 0.19) was significantly higher than that for asthma (4 ± 0.12; $p<0.0001$). Using a cutoff of 7, the questionnaire had a sensitivity of 87.6%, a specificity of 87.2%, and an area under the ROC curve of 0.95. Scores between 6 and 8 were observed in patients in whom the distinction between asthma and COPD was difficult to make (20% of patients).

The authors' concluded that given the small degree overlap between asthma and COPD, spirometry would add little to the discriminatory power of the questionnaire. Limitations of the study design were that it was retrospective, and included only patients with established diagnoses of asthma or COPD.

Table 10: Summary of findings for studies assessing history and clinical examination variables to distinguish between asthma and COPD.

Source and study design	Inclusion/exclusion criteria	Reference standard	Results
Beeh et al[27] Germany 2004 Retrospective study. Pulmonary specialist population.	Inclusion: ≥ 18 years with asthma and COPD.	Asthma: • FEV1<85%, and reversibility >12% and ≥200ml after bronchodilator, *or* • Positive histamine challenge and dry cough, wheezing and positive atopy status. COPD: • Post-bronchodilator GOLD criteria including symptoms, risk factor exposure.	N=547 Asthma: 62% Mean age: 33 yrs . Females: 57% COPD: 38% Mean age: 55yrs Females: 40% Predictors of COPD: • Age of onset • Male sex • Current smoking • Absence of atopy • Productive cough • No symptom variability
van Schayck et al[28] Netherlands 2005 Retrospective Population-based sample	Inclusion: ≥45 years	OAD: FEV1< 80% of predicted COPD FEV1/FVC ratio below lower limit of normal for age, sex and height. (If these criteria were not met, the patient was assumed to have asthma).	Multivariables: • Age • Smoking • Status • Pack years • BMI • Prior diagnosis of asthma or COPD or chronic bronchitis. • Chronic cough or phlegm
Tinkelman et al[29] Multicentre UK, USA 2006 Prospective Random mailing to primary care patients.	Inclusion: • ≥40 years • Prior diagnosis of OAD *or* on respiratory medications in previous year	COPD without reversibility: • Post-bronchodilator FEV1/FVC < 0.70, *and* • Reversibility < 200mL or < 12% of baseline FEV1. COPD with reversibility: • Post-bronchodilator FEV1/FVC < 0.70, *and* • Reversibility ≥200mL or ≥12% of baseline FEV1 Asthma: • Post-bronchodilator FEV1/FVC ≥ 0.70, *and* • Reversibility ≥200mL or ≥12% of baseline FEV1 Probable asthma: • Post-bronchodilator FEV1/FVC ≥ 0.70, *and* • Reversibility < 200mL or < 12% of baseline FEV1, *and* prior diagnosis of asthma or chronic use of corticosteroids. Probable asthma: • Post-bronchodilator FEV1/FVC ≥ 0.70, *and* • Reversibility < 200mL or < 12% of baseline FEV1, *and* does not fulfill criteria for probable asthma.	N=597 Mean age: 59 years Females: 62% COPD with reversibility: 29% COPD without reversibility: 11% Asthma: 7% Probable asthma: 38% Probable normal: 15% Predictors of COPD (and scoring system) • Increasing age (40-49/50-59/60-69/70+) – 0/5/9/11 points, respectively. • Pack years (0-14/15-24/25-49/50+) – 0/3/7/9 points, respectively. • Worsening cough (no) – 1 point. • Breathing related disability (no) – 1 point. • Breathing-related hospitalisation – 6 points. • Worsening dyspnoea (yes) – 1 points. • Phlegm quantity > 15mL/d – 4 points. • Cold going to chest (yes) – 4 points. • Medications for breathing (yes) – 5 points.

Table 11: Scoring system for the distinguishing between asthma and COPD among patients ≥18 years* (from Beeh et al[27]).

Item	Score (points)
Age of onset (years)	
• < 20	0
• 20-40	1
• 40-60	2
• >60	3
Atopy	
• Yes	0
• None	4
Smoked pack years	
• 0	0
• 0-20	1
• 20-40	2
• > 40	4
Cough characteristics	
• Dry cough	0
• Productive cough	4

* A score of ≥8 indicates COPD.

In yet another study (**van Schayck et al**[28]) the aim was to determine which questions best predicted COPD in patients with OAD aged ≥45 years old. Questions were taken from a number of sources including published questionnaires and the GINA[9] and GOLD[11] guidelines. Data were retrospectively evaluated using information from a population-based database (n=1018). The definitions for COPD and asthma are presented in Table 10. The questions found to best distinguish between the two conditions were related to age, smoking status, BMI, pack years smoked, prior diagnosis of asthma, and chronic bronchitis or emphysema. Others were chronic cough (most days for 3 consecutive months and for at least 2 years) and phlegm (most days for 3 consecutive months and for at least 2 years). The presence of these items produced a sensitivity of 72%, specificity of 64%, PPV of 68%, NPV of 68%, and ARUC of 0.74. A major limitation of this study was the criteria used to diagnose asthma (Table 10).

And finally, **Tinkelman et al**[29] aimed to determine which symptoms best identified COPD among smokers ≥40 years with no previous diagnosis of lung disease. The inclusion and diagnostic criteria are presented in Table 10. Each patient completed a self-administered questionnaire comprising 52 symptom-related questions. The predictors were derived from 70% of the sample (n=417), and then validated on the remaining 30%. The following were statistically different between those with and without COPD: phlegm in the morning (p=0.001), phlegm quantity (p<0.0001), phlegm production for 3 months of the year (p=0.003), wheeze frequency (p<0.0001), non-smoker asthmatic in the family (p=0.002), age-related breathing difficulties (p<0.0001), family history of allergies (p=0.042), reported past or present allergies (p=0.034), receiving treatment for allergies (p<0.0001), and reports that the patient tired more easily in recent years (p=0.019).

The predictors derived after multivariable analysis and their corresponding scores are presented in Table 10. The following items were included in the latter model: increasing age; cumulative pack years smoked; worsening cough in recent years; breathing-related disability (problems interfering with work and limiting the patient to the house or bed); hospital admissions for breathing problems; worsening dyspnoea in the past few years; phlegm quantity; chest problems when the patient has a cold; and use of medications to help with breathing. The derived predictors yielded a sensitivity of 72% and a specificity of 83%, with a ARUC of 0.84. As part of a related study, **Price and Tinkelman et al**[30] devised a scoring system for the derived predictors (Table 10).[§]

Strengths of the study were the large sample size and the consecutive data collection. Potential limitations were that the GOLD definitions of COPD could have overestimated the number of patients ≥70 years with this condition, and the low response rate to the posted questionnaire.

In summary, studies to determine the best clinical items to predict COPD in patients with OAD regardless of the age of the patient suggests that increasing age, smoking

[§] The scoring system is presented as part of the data in the table.

status, cumulative pack years, chronic cough and phlegm production are most suggestive. In one study,[29] breathing-related variables such as hospitalisation, worsening of dyspnoea over time, worsening of symptoms during a upper respiratory tract infection, and use of medications for breathing were additional predictors. The inclusion of breathing-related variables in the latter study could be attributed to the larger number of symptom-related items (52 items) included in their questionnaire. Sensitivities and specificities of the questionnaires ranged from 72%-87% and 64%-87%, respectively. And areas under the ROC curve ranged from 0.74 to 0.95, indicating a high degree of accuracy. These results support the use of symptom and sign based questionnaires to aid in the differential diagnosis of OAD and in case-finding for COPD.

4.4 ASTHMA

4.4.1 Clinical features in patients with asthma

Wheezing and nocturnal dyspnoea are strongly correlated with asthma[31] and wheezing is the commonest symptom in patients with this condition. A questionnaire-based (European Community Respiratory Health Survey questionnaire) [32] study, of respiratory symptoms as predictors of asthma, was conducted in Switzerland by **Sistek et al.**[33] Randomly selected patients aged 18-60 years old were studied. Asthma was diagnosed if responses to each of the following questions were positive: (1) self-reported asthma (2) physician-confirmed asthma (3) asthma attack in the last 12 months. The prevalence of asthma was 2.3% (225 of 9651 patients), and 14% reported a wheeze of any form (in the last 12 months; associated with breathlessness; in absence of a respiratory tract infection).

Wheezing (wheezing alone (94.4%), wheezing with dyspnoea (87.6%), wheezing without cold (79.8%)) was the most prevalent symptom in asthmatics (75%), followed by dyspnoea on exercise (82%), and nocturnal symptoms (chest tightness (67.4%) and dyspnoea (68.5%). The presence of chronic sputum production (43.8%), cough (42.7%), and bronchitis (24.7%) were least commonly reported.

Individual symptoms which best predicted asthma were wheezing (wheezing alone, wheezing with dyspnoea, wheezing without cold), nocturnal chest tightness, dyspnoea and nocturnal cough (Table 12). Chronic cough, sputum production and bronchitis performed worst at predicting asthma. Wheezing with dyspnoea had the highest PPV (23.9%) and a specificity of 95.1%, compared to wheezing alone (12.4% and 97.3%, respectively). Wheezing with dyspnoea was therefore identified as the best individual symptom to predict asthma. Individual nocturnal symptoms and cough were poor predictors of asthma. The likelihood ratio for each symptom was calculated by the author of this thesis.

Of the symptom combinations (as determined by multivariate analysis), wheezing with two of the three following nocturnal symptoms best predicted asthma: dyspnoea, chest tightness, and cough. The sensitivity of this combination of symptoms was 80%, the specificity (85.9%), the PPV (11.9%), the NPV (99.4%), and the Youden index, which is a measure of accuracy, was 0.66 (Table 13).

Table 12: Diagnostic characteristics of individual symptoms (from Sistek et al33).

INDIVIDUAL SYMPTOMS	SENS	SPEC	PPV	NPV	YOUDEN INDEX*	LR+**
Wheezing	75	87	12	99	0.62	5.76
Wheezing with dyspnoea	65	95	24	99	0.60	13
Wheezing without cold	60	94	18	99	0.53	10
Nocturnal chest tightness	49	86	8	99	0.63	3.5
Rest dyspnoea	47	95	18	99	0.42	9.4
Exercise dypnoea	69	76	6	99	0.45	2.9
Nocturnal dypnooea	46	96	22	99	0.42	11.5
Nocturnal cough	49	73	4	98	0.22	1.8
Chronic cough	22	95	10	98	0.17	5.5
Chronic phlegm	23	93	8	98	0.16	3.3
Chronic bronchitis	13	98	14	98	0.11	6.5

Sens: sensitivity; spec: specificity; PPV: positive predictive value; NPV: negative predictive value; LR: positive likelihood ratio.

* Youden index=(sensitivity.specificity)-1. The closer the index is to one, the better the diagnostic value of the item.

** Positive likelihood ratio calculated for the purposes of this review.

The authors' caution that the results of the study may be biased as it is an epidemiological study and may therefore not be generalisable to clinical practice. The use of self-reported, physician-confirmed asthma and a history of an asthma attack, as the reference standard, was said to be a relatively robust proxy for a definitive diagnosis of asthma, thereby increasing the certainty of a true diagnosis. A criticism is that patients without a recent asthma attack or doctor diagnosis could have been excluded, or that patients with a recent history of exacerbation may have had more severe disease, thus limiting the applicability of the findings. Due to the low specificity of bronchial hyper-responsiveness testing it was not used as a reference standard.[34 35]

Table 13: Summary of findings for studies assessing history and clinical examination variables as predictors of asthma.

Source and study design	Inclusion/exclusion	Reference standard	Results
Sistek D et al[33] Switzerland 2001 Cross-sectional (random selection) General population.	Inclusion: • 18-60 years • Current asthma	Current asthma: • Self-reported, *and/or* • Physician-diagnosed, *and/or* • Asthma attack in last 12 months.	N=9651 Mean age and sex distribution: not provided. Asthma: 2.3% Predictors (individual) symptoms: Wheezing with dyspnoea Predictors (combinations) of symptoms: Wheezing and 2 of 3 nocturnal symptoms (cough, dyspnoea, tight chest)
Sistek et al[36] New Zealand year 2006 Cross-sectional General population.	Inclusion • 20-44 years • Current asthma	Current asthma: • Self-reported, *and/or* • Physician-diagnosed, *and/or* • Asthma attack in last 12 months.	N=1257 Mean age: 35years Females: 37% Doctor-diagnosed asthma: 8.3% Predictors of asthma: • Wheeze with dyspnoea • Wheeze alone
Bai et al[37] Australia Cross-sectional General population	Inclusion: 18-55 years	No definitive reference standard used. BHR: • FEV1 ≥60%of predicted and ≥20% fall in FEV1 at maximum dose of histamine, *or* • FEV1<60% of predicted and ≥15% reversibility after bronchodilator challenge.	N=1527 Mean age: not provided. Females: 58%. Items most strongly correlated with asthma: • Wheeze in the last 12 months. • Asthma attacks. • Chest tightness. • Recent nebuliser use. • Wheeze following exercise. • Dyspnoea at rest.
Burrows et al[39] United States. 1991 Long term prospective (longitudinal) study. General population.	Inclusion: • >60 years • Newly-diagnosed asthma Exclusion: • Patients with previous diagnosis of self-reported, *or* • Physician diagnosed asthma, or COPD excluded.	Newly-diagnosed asthma: Reported doctor-diagnosed asthma on follow-up	N=1185 Mean age: 64 years Females: 61% Newly-diagnosed asthma: 3.4% Predictors of asthma: • Any wheezing compliant, and/or • Attacks of shortness of breath and wheezing.

In a second study by **Sistek et al**[36] aimed to assess the diagnostic accuracy of selected respiratory symptoms, and whether the presence of bronchial hyper-responsiveness (BHR) improved the predictive value of the symptoms. Data were collected by means of the ECRHS questionnaire. The reference standard definition is presented in (Table 13). Of the 1257 subjects aged 20-44 years, 784 (62%) underwent BHR testing using methacholine, 8.3% had doctor-diagnosed asthma; and 30% wheezed in the last 12 months.

The most prevalent items were nocturnal symptoms (44%), nocturnal cough (36%), wheezing (30%), exercise dyspnoea (28%), and bronchial hyperresponsiveness (25%). The least prevalent symptoms were: nocturnal dyspnoea (7%), chronic bronchitis (8), and chronic phlegm production (13%). Symptoms predictive of doctor-diagnosed asthma were wheezing with dyspnoea, wheezing, BHR, and wheezing without a cold (Table 14). Chronic cough and chronic phlegm production were least predictive of asthma. For the purpose of this review, likelihood ratios for each item have been calculated.

The combined symptoms of wheeze, wheeze with dyspnoea, nocturnal dyspnoea, nocturnal chest tightness, and exercise dyspnoea were the strongest and most significant predictors of asthma when adjusted for age, gender, ethnicity and current smoking. Adding BHR to each symptom significantly increased the specificity of all the symptoms, and significantly decreases the sensitivity for all symptoms except for nocturnal dyspnoea, chronic bronchitis, and chronic phlegm production (production of phlegm in the mornings in winter). But overall the addition of BHR adds little additional value to the diagnosis meaning that wheeze with dyspnoea and wheeze alone are the best predictors.

Table 14: Value of symptoms to predict asthma. All symptoms present in last 12 months (from Sistek et al36).

SYMPTOM	SENS	SPEC	PPV	NPV	Youden index**	LR+[#]
Wheezing	94	76	28	98	0.65	3.9
Wheezing with breathlessness	82	90	26	99	0.70	8.2
Wheezing or dyspnoea without an URTI	77	87	43	98	0.72	5.9
Nocturnal dyspnoea	42	96	35	98	0.64	10.5
Nocturnal chest tightness	75	85	47	95	0.37	5
Nocturnal cough	60	66	31	98	0.61	1.8
Dyspnoea at rest	43	93	14	95	0.26	6
Dyspnoea on exercise	75	77	35	95	0.36	3.3
Chronic cough	43	84	23	97	0.52	2.7
Chronic phlegm production in morning in winter	26	88	19	94	0.27	2.2
Chronic bronchitis	22	93	17	93	0.15	3.1
Nocturnal symptoms*	83	59	22	93	0.15	2.0

Sens: sensitivity; spec: specificity; PPV: positive predictive value; NPV: negative predictive value; LR: positive likelihood ratio.
* Nocturnal symptoms refer to: nocturnal cough, dyspnoea, and chest tightness.
** Youden index = (sensitivity.specificity)-1. The closer the index is to one, the better the diagnostic value of the item.
[#] Likelihood ratio calculated for the purposes of this review.

Another study conducted by **Bai et al**[37] set out to examine which questionnaire items from the shortened version of the IUATLD (International Union against Tuberculosis and Lung Disease)[38] questionnaire best predicted asthma and other respiratory 'syndromes' in 1572 adults by determining which questionnaire items were highly correlated with each another. The correlated items were then examined to determine the 'syndrome' they represented. These syndromes were validated using history, examination and physiological factors (eg. BHR, atopy, lung function, smoking status, and body mass index (BMI)) associated with asthma and other respiratory conditions.

BHR was defined as a ≥20% fall in the maximal dose of histamine (only performed if FEV1 ≥60% of predicted), or ≥ 15% reversibility after bronchodilator testing (only performed if FEV1<60% of predicted).

Analysis of the questions identified four syndromes (asthma, cough, urgent medical visit, and breathlessness). Table 15 lists the questionnaire items (symptoms) which best correlated with each identified syndrome. Patients were placed into each group according to their symptoms, and a fifth group (normal) was added to the analysis. The question 'woken by cough' did not fit into any of the groups. Wheeze in the last 12 months, asthma attack and chest tightness were shown to have the strongest correlation with asthma, followed by recent nebuliser use, wheeze following exercise and shortness of breath at rest. The authors therefore suggest that these items be considered in epidemiological studies. The increased prevalence of BHR in the asthma group supports the diagnosis of asthma in patients with these symptoms.

Table 15: Questionnaire items correlated with respiratory disease syndromes. (from Bai et al[37]).

Syndrome	Questionnaire items	Percentage in whom BHR demonstrated
Asthma (33.8%) (if one or more symptoms present, "regardless of cough or breathlessness status")	Wheeze in last 12 months Asthma attack Chest tightness Recent nebuliser use Wheeze following exercise Chest tightness on waking	77% * (and atopy p<0.001 when compared to the other groups)
Urgent medical visit (if one or more symptoms present) (10.1%) (Over 95% of patients were also in the asthma group, and therefore it was considered to be a subset of asthma.)	Hospitalisation Casualty department visit Urgent doctor visit	(included in asthma syndrome)
Cough (7.7%) (if one or more symptoms present and negative to asthma)	Morning cough Cough for 3 months per year Usual cough Cough with phlegm	4.2%
Breathlessness (5.1%) (if one or more symptoms present and negative to asthma and cough)	Breathlessness on waking Breathlessness on exertion	1.7%
Normal (53.5%) (no positive answers)	No abnormalities reported	17.5%

4.4.2 Clinical features of asthma in patients 60 years and older

Burrows et al[39] conducted a study in newly-diagnosed asthmatics aged 60 years and older to describe their clinical features at the time of diagnosis. This longitudinal prospective study based on repeated questionnaires studied 1185 patients with no history of asthma or COPD and established a new diagnosis of asthma in 3.4% of patients.

When comparing the newly-diagnosed asthmatics with the remaining study population, the combination of any wheezing and/or attacks of shortness of breath

with wheezing was the most prevalent symptom (63% vs 23%) and highly predictive of newly-diagnosed asthma (relative risk (RR) 5.1 (95% CI: 2.7-9.5). Wheeze (any form[§]) was the second most prevalent symptom (50% vs 20% in non-asthmatics) and strongly predicted a diagnosis of asthma (RR 3.8 (95% CI: 2.1-6.9). Attacks of shortness of breath with wheezing was only reported in 37.5% of newly-diagnosed asthmatics patients compared to 11% of the controls, and it also strongly predicted the presence of asthma (RR 4.4 (95% CI: 2.4-8.2)). Chronic cough (20%), chronic sputum production (28%), and chronic cough and/or sputum production (28%) were least prevalent and poorly predicted the presence of asthma (RR 1.3 (95% CI: 0.6-2.9), 2.2 (95% CI: 1.1-4.2), and 1.4 (95% CI: 0.7-2.9), respectively).

Both wheezing (all forms) and attacks of shortness of breath with wheezing were the best single predictors of newly-diagnosed asthma using multiple logistic regression analysis. Other predictive history variables were: current allergic rhinitis (prevalence 65% vs 36%; RR 3.1 (95% CI: 1.7-5.9) and "respiratory trouble before age 16" (prevalence 35% vs 15%; RR 2.9 (95% CI: 1.5-5.4). There was no statistical difference with regards to smoking habits, but significantly more patients with newly-diagnosed asthma smoked < 10 pack years ($p<0.05$).

Clinical features of the newly-diagnosed patients were also compared to those who were assessed as having COPD. No significant differences between the two groups were found except for initial wheezing, and reported allergic rhinitis without or without a positive skin prick test. Results show that symptoms started 8 years before onset of newly-diagnosed asthma if ≥ 60 years old, and a rapid decline in lung function around the time of diagnosis suggests asthma. A limitation of the study was that BHR was not performed on the patients. Serum IgE levels were also analysed, but these were not reported in this review.

In summary, wheezing with or without breathlessness and nocturnal dyspnoea were the strongest predictors of asthma regardless of age when detecting asthma in young and old.

[§] Wheezing (all forms) includes wheezing alone or wheezing associated with: not associated with colds, dyspnoea, attacks of wheezing.

4.5 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

4.5.1 Clinical features predicting COPD

Badgett et al[40] claims to have conducted the first study to determine which symptoms and signs best predict COPD. Ninety-two current or former smokers ≥40 years old with self-reported COPD were recruited from hospital outpatient clinics. They completed a questionnaire, were examined by physicians blinded to the history, and underwent lung function testing. The criteria for moderate COPD diagnoses (16%) are shown in Table 16.

Table 16: Summary of findings for studies assessing history and clinical examination variables as predictors of COPD.

Source and study design	Inclusion/exclusion	Reference standard	Results
Badgett et al[40] **USA** **1993** Prospective (consecutive). Recruited by notices in hospital clinic. Self-administered questionnaire for history.	Inclusion: • ≥ 40 years, current/former smoker, *or* • Previous asthma, chronic bronchitis, or emphysema.	Moderate COPD: • FEV1<60% of predicted or ratio <0.6. Ratio could not be 0.8 or more with FVC less than 80% of predicted.	N=92 Mean age: 56 years Females: 47% Predictors of COPD: • ≥70 pack years + reduced breath sounds
Straus et al[41] **Multicentre; 25 study sites in 4 countries.** **2000** Prospective (consecutive) via internet. Primary care and referral settings.	Inclusion: • ≥18 years • Known COPD • Spirometric COPD (FEV1 and FEV1/FVC ratio below the fifth percentile) OR • Self-reported (COPD, chronic bronchitis, emphysema, inhaled bronchodilators and/or inhaled steroids) *OR* • Suspected COPD	COPD: • FEV1 below the fifth percentile.	N=309 Mean age: 56 years Females: 43% Predictors of COPD: • Self-reported COPD • 40 pack years • 45 years • Maximum laryngeal height ≤ 4 cm
Straus et al[42] **Multicentre study ;7 study sites in 6 countries.** **2002** Prospective (consecutive) via internet. Primary and secondary care settings.	Inclusion: • ≥50 years • Known COPD: • Spirometric COPD (FEV1 and FEV1/FVC ratio below the fifth percentile) OR • Self-reported (COPD, chronic bronchitis, emphysema, inhaled bronchodilators and/or inhaled steroids) *OR* • Suspected COPD Exclusion • Asthma • Medically unstable	COPD: FEV1 and FEV1/FVC ratio below the fifth percentile.	N=161 Mean age: 64 years. Females: 62% females Predictors of COPD • Self-Reported history of COPD • Wheezing • FET ≥9 seconds

Freeman et al[43] **UK** **2005** Retrospective database analysis Primary care	Inclusion: • ≥40 years • using respiratory medications in previous 2 years. • History of smoking • Asthma based on medical history but not on medications Exclusion: • FEV1/FEV < 70% of predicted with reversibility or clinical impression of asthma. • Known respiratory diseases.	COPD: • FEV1/FVC < 70% and no reversibility. Asthma: • Reversibility and clinical impression No OAD: • FEV1/FVC ≥70% of predicted and no evidence of OAD.	N=369 Mean age: 61.7 years Females: 8% Predictors of COPD: • Increasing age. • Cough occasionally or more frequently. • Dyspnoea on exertion. • Daily wheezing.
Price et al[44] **Multicentre** **UK, USA** **2006** Prospective Random mailing to primary care patients.	Inclusion: • ≥40 years • No prior diagnosis of OAD *or not* on respiratory medications in previous year	COPD without reversibility: • Post-bronchodilator FEV1/FVC < 0.70, *and* • Reversibility < 200mL or < 12% of baseline FEV1. COPD with reversibility: • Post-bronchodilator FEV1/FVC < 0.70, *and* • Reversibility ≥200mL or ≥ 12% of baseline FEV1. Asthma: • Post-bronchodilator FEV1/FVC ≥0.70, *and* • Reversibility ≥200mL or ≥ 12% of baseline FEV1. Probable asthma: • Post-bronchodilator FEV1/FVC ≥0.70, *and* • Reversibility < 200mL or < 12% of baseline FEV1, *and* prior diagnosis of asthma or chronic use of corticosteroids. Probable asthma: • Post-bronchodilator FEV1/FVC ≥0.70, *and* • Reversibility < 200mL or < 12% of baseline FEV1, *and* does not fulfill criteria for probable asthma.	N=798 Mean age: 58 years Females: 51% COPD with reversibility:: 29% COPD without reversibility: 11% Asthma: 7% Probable asthma: 38% Probable normal: 15% Predictors of COPD (and scoring system) • Increasing age (40-49/50-59/60-69/70+) – 0/4/8/10 points, respectively. • BMI (< 24, 25-29, >30) – 5/1/0. • Pack years (0-14/15-24/25-49/50+) – 0/2/3/7 points, respectively. • Weather affects the cough (yes) – 3 points. • Sputum production when you don't have a cold (yes) – 3 points. • Sputum production first thing in the morning (no) – 3 points. • Frequency of wheeze (occasionally or more often/never) – 4 points. • Reported allergies (no) – 3 points.
van Schayck et al[28] **Netherlands** **2005** Retrospective Population-based sample	Inclusion: ≥45 years	COPD: • FEV1/FVC below lower limit of normal (age, sex, height)	Multivariables: • Age • Smoking • Status • Pack years • BMI • Prior diagnosis • Chronic cough or phlegm for three months.

The individual symptoms significantly associated with a diagnosis of COPD are shown in Table 17. Likelihood ratios have been added for the purpose of this review. Diminished breath sounds was the best univariable predictor of COPD (sensitivity 65%, specificity 96%, PPV 77%, NPV 93%).

Table 17: Significant predictors of COPD on univariable analysis (from Badgett et al[40]).

UNIVARIATE ANALYSIS VARIABLES (statistically significant)	SENS (%)	SPEC (%)	PPV (%)	NPV (%)	LR+
History variables					
Age ≥ 75 years	13	99	67	85	13
Previous diagnosis of COPD (y/n)	80	74	38	95	3.1
Smoke	40	95	60	89	8.0
Shortness of breath when bathing, dressing, or at rest	60	75	32	91	2.4
Phlegm ≥ ¼ cup or morning in morning	20	95	43	85	4.0
Theophylline use	60	71	29	90	2.1
Steroid use	40	87	38	88	3.1
Inhaler use	27	94	44	87	4.5
Home oxygen	20	96	50	86	5.0
Physical examination*					
Auscultatory percussion	32	94	50	87	5.3
Cardiac dullness	16	99	69	85	16
Reduced breath sounds	65	96	77	93	16
Forced expiratory time ≥ 11 seconds (mean)	12	99	57	85	12
Initial impression	25	95	50	86	5.0
Final opinion	51	93	60	91	7.2
Wheezes	9	100	83	85	0.0

* Not all variables included in study are included in the table.

Combinations of history and examination variables which best predict COPD are presented in Table 18. When assessing the sequential addition of multivariate predictors for history variables alone, the only history variables entered into the model

were self-reported history of COPD and pack years history ≥ 70 (Model A). When the blinded physical examination variables were entered into the model, then diminished breath sounds was the only significant variable to enter the model of all four examiners (Model B). Finally, a peak flow of < 200L/ml was added to Model B and increased its sensitivity to 77%, and the area under the ROC curve (ARUC) to 0.90 (sensitivity 77%, specificity 95%). Because of the small difference between models A and B, the investigators felt that peak flow measurements (Model C) in fact added very little to the history and physical examination variables and should not be used in the diagnosis of COPD.

Limitations of the study are that it only tested moderate and not mild or severe disease; and no distinction was made between reversible and irreversible disease. A strength may be that the physicians' were not privy to history findings prior to examination and this may have reduced incorporation bias. According to the method of analysis, the ≥ 70 pack year cut-off was generated to give the lowest misclassification rate but this value is quite high. However, 13% of the sample had never smoked and 30% with an average pack year history of ≥40 years.

Table 18: Predictive abilities of a combination of symptoms and signs (from Badgett et al[40]).

MODEL	VARIABLES	Sens, (%;95%CI)	Spec, (%;95%CI)	LR+ (95%CI	ARUC
A	Self-reported history of COPD and pack years history ≥ 70	40	100	Infinite	0.80
B	Self-reported history of COPD and pack years history ≥ 70, plus decreased breath sounds	67 (58-80)	98 (97-100)	38 (22.5-infinite)	0.88
C	Self-reported history of COPD and pack years history ≥ 70, plus decreased breath sounds, plus Peak flow meter reading < 200L/min	77 (73-87)	95 (95-97)	16.9 (13.8-22.1)	0.90

Sens: sensitivity; spec: specificity; PPV: LR+: positive likelihood ratio; ARUC: area under the receiver operating characteristic curve.

A second study to determine the accuracy of selected features (self-reported COPD, wheezing, laryngeal height, and laryngeal decent) in diagnosing COPD was conducted by **Straus et al.**[41] This multicentre study assessed consecutive patients ≥18 years (n=309) with: (1) self-reported, or (2) suspected COPD, or (3) spirometrically confirmed COPD. About half (52%) had COPD as defined according to the reference standard (Table 16). The only variables significantly predictive of COPD on univariable analysis were: known COPD (LR+ 12.9), > 40 pack years smoking history (LR+ 19.1), age 45-64 years (LR+ 1.5), presence of wheezing (LR+ 2.7), and maximum laryngeal height ≤ 4cm (LR+ 1.5). Of these, only 4 items were included in the reduced multivariable model (wheeze not included). The likelihood of COPD in a patient with all 4 items was 220.5. Even at varying spirometric definitions of COPD these results were not shown to change much.

The authors' argue that inclusion of self-reported history in the prediction rule reflects the role it plays in history taking and its accuracy in clinical practice. Even on its exclusion from the model, the utility of the other variables for detecting COPD in undiagnosed patients at presentation was the same. This study is one of the first to include a larger number of patients and clinicians (46 investigators), and to evaluate consecutive patients, thereby decreasing bias. But the model was not subsequently validated, thereby decreasing its generalisability to other populations.

Table 19: Multivariable predictors (adjusted likelihood ratios) of COPD (from Straus et al[41]).

Item	All patients with COPD		Patients with known COPD excluded	
	LR+	LR-	LR+	LR-
Self-reported COPD	7.3	0.5	-	-
40 pack years	8.3	0.8	11.6	0.9
Age ≥45 years	1.3	0.4	1.4	0.5
Maximum laryngeal height ≤ 4cm	2.8	0.8	3.6	0.7
All factors	220.5	0.13	58.5	0.32

A third study also conducted by **Straus et al**[42] aimed to determine the accuracy of self-reported COPD, smoking status, number of pack years smoked, wheezing on auscultation, and forced expiratory time (duration of forcible exhalation after maximal inhalation) to diagnose COPD in patients ≥50 years old presenting in primary and secondary care. ROC curve analysis determined a cut-off of 40 pack years for smoking, and 6 and 9 seconds for forced expiratory time for inclusion in the model. Multivariate logistic regression analysis showed that the items that best predicted COPD were: self-reported history of COPD, audible wheezing heard on auscultation, and a forced expiratory time of greater or equal to 9 seconds (Table 20). The cumulative adjusted likelihood ratio[§] for making the diagnosis of COPD if all three factors were present is 59. The reported strengths and limitations of this study are similar to those reported for their first study[41]

[§] The cumulative likelihood ratio is calculated by multiplying the likelihood ratios for all, or selected, variables included in the multivariable model.

Table 20: Multivariable predictors (adjusted likelihood ratios) of COPD. (From Straus et al[42])

DIAGNOSTIC ELEMENTS	ADJUSTED LIKELIHOOD RATIO	
	FACTOR PRESENT	FACTOR ABSENT
Self-reported history of COPD	4.4	0.5
Wheezing	2.9	0.8
FET ≥ 9 seconds	4.6	0.8

The second last study to be reviewed in this chapter was conducted by **Freeman et al**[43] who determine the value of individual questions in identifying patients ≥40 years with COPD in primary care settings. History and spirometric data were collected on all included patients, but reversibility testing was only conducted on patients who used medications, those who had asthma, and smokers with a FEV1 < 80% (Table 16). On bivariate analysis: age > 55 years, former smokers, reported cough, dyspnoea and wheeze were significantly associated with COPD compared to not having COPD, but no difference between pack years smoked was shown. Two multivariable models were evaluated: (1) a model containing variables with multiple responses (2) a model containing collapsed variables (Table 21). On multivariable analysis, the odds of having COPD were greater if older than 70 years, dyspnoeic when climbing stairs or on light exercise, and daily wheezing. When the categories for each variable were collapsed, age ≥70 years, cough, dyspnoea on exercise to rest were most predictive. When assessing the best combination of symptoms as measured by the area under the ROC curve, the model containing questions with multiple responses performed slightly better than the one requiring mostly 'yes/no' answers (ARUC: 86% vs 85%).

The authors concluded that increasing age, occasional or frequent cough, dyspnoea on exertion, and daily wheezing were strong predictors of COPD among high-risk patients; and that their results supported the use of wheeze as a symptom to predict COPD. Limitations of the latter study were that they excluded smokers on medications, and used FEV1 < 80% of predicted as the definition of airways obstruction. Results also suggest that the questions perform much better with

increasing severity of COPD. Other limitations could have been diagnostic misclassification leading to the inclusion of asthmatics, the retrospective nature of the study, and the high smoking burden that might have resulted in the exclusion of pack year history from the model.

Table 21: Multivariable predictors and the diagnostic accuracy of two models to predict COPD (from Freeman et al[43]).

ITEM AND CATEGORIES	ODD RATIO*	CATEGORIES	ODD RATIO*
Model 1 (multiple responses)		**Model 2 (collapsed responses)**	
Age (years)		**Age (years)**	
40-54	1.0 (ref)	• 40-54	1.0 (ref)
55-69	4.5 (1.2-17)	• 55-69	4.6 (1.3-16)
70+	16 4.4-61)	• 70+	21 (6.1-73)
Smoking status			
Former smoker	1.0 (ref)		
Current smoker	0.6 (0.28-1.3)		
Pack years		**Pack years**	
0-19	1.0 (ref)	0-19	1.0 (ref)
20+	1.3 (0.62-2.9)	20+	0.93 (0.47-1.8)
Cough		**Cough**	
None	1.0 (ref)	None	1.0 (ref)
Occasional	0.94 (0.31-2.9)	Occasional or more often	2.4 (1.2-4.7)
Only with exacerbations	3.1 (0.98-9.9)		
Most mornings	2.2 (0.75-6.2)		
Every day	1.8 (0.65-5.0)		
Dyspnoea		**Dyspnoea**	
None	1.0 (ref)	None	1.0 (ref)
Only with vigorous exercise	3.1 (0.95-10.4)	On any exercise or at rest	3.0 (1.5-5.9)
On climbing stairs	4.8 (1.5-15.2)		
On light exercise	8.3 (2.6-26)		
At rest	2.4 (0.50-12)		
Wheeze		**Wheeze**	
None	1.0 (ref)	None or less that every day	1.0 (ref)
Occasional	1.2 (0.54-2.7)	Every day wheeze	2.2 (0.89-5.5)
At least once/week	1.3 (0.35-4.8)		
Every day	3.1 (1.1-9.5)		
Sensitivity 77.4%		Sensitivity 87.1%	
Specificity 76.2%		Specificity 71.3%	
PPV 39.7%		PPV 38.0%	
NPV 94.4%		NPV 96.5%	
Area under ROC curve 85.9%		Area under ROC curve 85.0%	

*Odds of having COPD.

Sens: sensitivity; spec: specificity; PPV: LR+: positive likelihood ratio; ARUC: area under the receiver operating characteristic curve.

As part of the same study conducted by Tinkelman et al[29] (reported above) in which the predictors to distinguish asthma from COPD were determined, **Price et al**[44] assessed the symptoms that best identified COPD in smokers. Patients ≥40 years with no previous respiratory diagnoses, and those not using medications in the past year were enrolled. The diagnostic criteria used in the study were the same as that presented in Table 16. Each patient completed a self-administered questionnaire comprising 52 symptom-related questions. The predictors were derived from 70% of the sample (n=417), and were validated on the remaining 30%. The following were statistically different between those with and without COPD: age ($p<0.0001$), male sex ($p=0.006$), BMI ($p=0.0004$), smoking intensity as measured in pack years ($p<0.0001$), recent onset of dyspnoea ($p=0.028$), sputum production in the absence on an URTI (0.001). Regression analysis produced a model containing the following questions to predict COPD: age; smoking intensity; low body mass index, cough worsened by the weather, sputum production in the absence of a URTI, wheezing occasionally or more often, and no reported allergies. The derived predictors yielded a sensitivity of 80% and a specificity of 72%, with an ARUC of 0.82. As part of a related study, **Price and Tinkelman et al**[45] devised a scoring system for the derived predictors which is presented as part of the data in Table 16.

And finally, the same study reported above by **van Schayck et al**[28] (Table 16) compared predictors of COPD using patients assessed as not having COPD as the comparator. Results revealed that age, BMI, smoking status, number of pack years smoked, previous diagnosis of asthma, chronic bronchitis or emphysema, frequent cough , and duration of cough ≥2 years; or frequent phlegm production (most days for 3 consecutive months) and phlegm production for ≥2 years. These questions yielded a sensitivity of 71%, specificity of 67%, PPV of 25%, NPV of 94%, and an ARUC of 0.75.

In summary, a history of smoking, cumulative pack year history, a previous diagnosis of COPD, cough-related variables, and sputum production are the best predictors of COPD among patients older than 40 years. Only one study[42] was conducted in patients older than 18 years, and results supported the use of smoking history, cumulative pack years and age older than 45 years as predictors.

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Chapter 5 : METHODS AND MATERIALS: Development of the PALSA guideline and intervention support materials

5.1 Overview of the chapter

In this chapter, the methods used to develop the PALSA guideline will be presented. It is important to note that although each development step is presented separately, the overall development process was iterative with each step informing the other and often occurring concurrently.

The five phases were as follows:

- Formation of a multidisciplinary guideline development group.
- Review of relevant policy documents, guidelines and literature.
- Qualitative research
    - Structured reflection and brainstorming.
    - Face-to-face interviews.
    - Focus group discussions.
- Development of the printed guideline support materials and training programme (intervention strategy).
- Piloting of the PALSA intervention strategy.

These methods are discussed in more detail below.

5.2 Formation of a multidisciplinary guideline development group

The aim was to form a multidisciplinary guideline development group comprising members with a wide range of experiences, interests, and skills. This group was assembled by EDB and MFZ. At the first meeting the aims of the PALSA guideline and development process the roles and responsibilities of each member, the methods

to be employed during the development process, and time lines were discussed. The author of this thesis took the lead in the development process.

5.3 Review of relevant policy documents, guidelines and literature

5.3.1 Review of local policy documents

The team reviewed available national policies and documents outlining primary health care in South Africa in order to determine the following:

- The national framework and strategies for primary health care implementation.
- Human and physical resource availability at local clinics and within the district health system.
- The role, scope of practice (including prescribing provisions), and support of nurses involved in primary health care.
- Organisational logistics relating to the district health system, for example, referral patterns and management structures.

5.3.2 Review of relevant local and international guidelines

Relevant international and national respiratory guidelines were reviewed. These guidelines were retrieved by electronic search (MEDLINE, websites of well-known international respiratory societies, large international organisations, guideline development agencies, and departments of health websites), and by contacting local experts, frontline clinicians and managers. More information on the details of these organisations will be provided in the chapter that follows.

5.3.3 Review of the medical literature

Relevant published literature was reviewed to determine local respiratory epidemiological patterns and to identify studies on the diagnosis and management of the respiratory conditions to be included in the PALSA guideline. The guideline development group chose not to conduct their own systematic reviews because of resource and time constraints, but instead considered those reviewed by others (secondary research). [1] Articles were identified through electronic searching (MEDLINE, the Cochrane Collaboration Database, [2] evidence-based guidelines published by guideline development agencies) and through hand searching references in retrieved articles, and by contacting local respiratory experts.

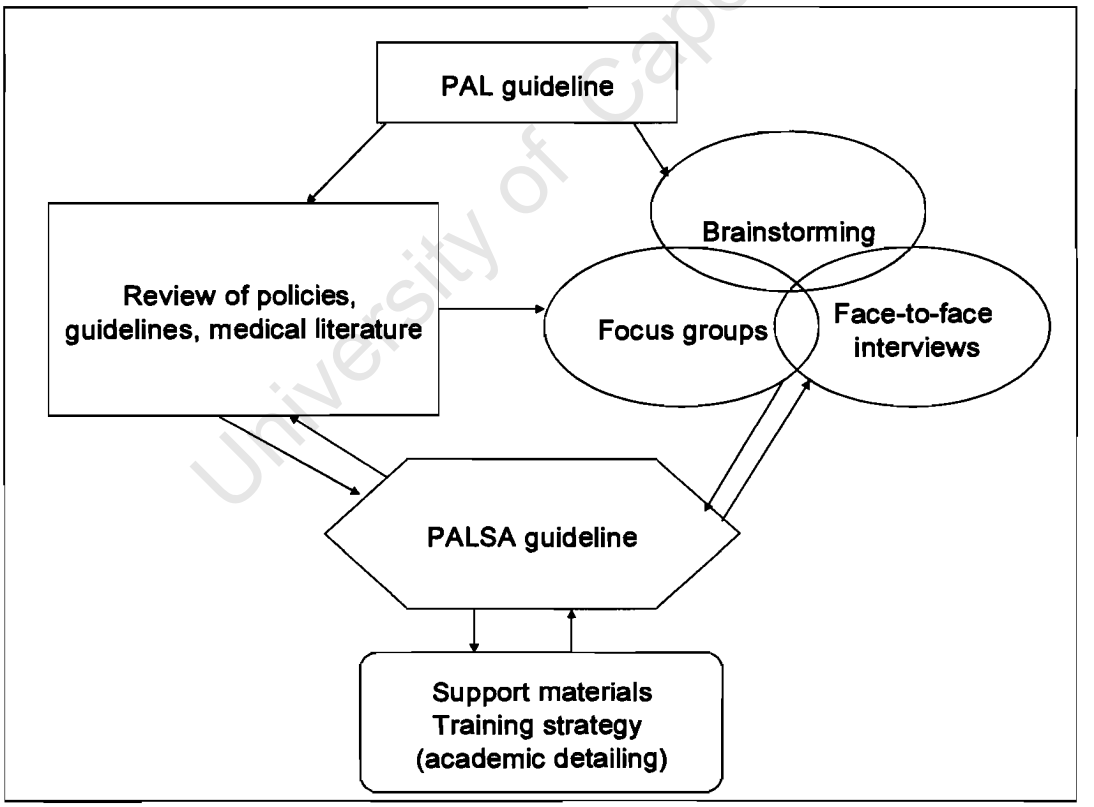
5.4 Qualitative research methods

Qualitative research is one of the best methods to use for exploring opinions, attitudes and behaviors.[3] The qualitative methods employed in this study were used to (1) evaluate the generic PAL guideline (2) determine barriers to the delivery of quality respiratory disease care, and (3) inform the tailoring of the guideline and its support materials to address identified barriers and to match local practices and resource availability. A variety of methods were employed, as methodological triangulation (obtaining information by using a variety of qualitative methods) has been shown to strengthen the reliability of qualitative research findings, and ensures comprehensiveness of the collected data.[4 5]

Brainstorming is shown to stimulate generations of new ideas. Focus groups are useful for accessing varied beliefs, knowledge and attitudes from groups of individuals within a limited time period.[6] It is also useful for facilitating generation of ideas. Face-to-face interviews provide the advantage of allowing a topic to be discussed with a great deal of flexibility, with opportunities for clarification of issues, and opportunities for offering conversational prompts, and for following up on new ideas.[7]

Brainstorming and feedback from the first focus group session were considered to be the exploratory phase of the PALSA guideline development. In this phase, the generic PAL guideline was discussed, and recommendations for its adaptation were presented. This process also served to assess the acceptability and to inform the development of the first draft of the PALSA guideline and its support materials, and to identify barriers to the delivery of quality respiratory disease care. The remaining focus group sessions, and the face-to-face interviews served to further inform the development of the PALSA guideline and the intervention materials. Details of these methods are presented in the sections that follow. Figure 1 illustrates how the combination of the methods described in this chapter informed the development of the PALSA guideline, its support materials, and the training strategy.

Figure 1: Illustration of how the qualitative methods informed the PALSA guideline and support materials development.



5.4.1 Brainstorming

Members of the guideline development group were asked to consider the concept, layout, presentation, and content of the PAL guideline, and to suggest ways in which

it could be adapted to the South African context. They were also asked about local barriers to the provision of quality respiratory care. This process was informal and relied on generation of ideas. The outcomes were recorded and analysed in the same manner and alongside that obtained from the remaining qualitative research (presented below).

5.4.2 Focus group discussions

The aims of the focus group discussions were the same as the overall aims of the qualitative research as presented above. Three focus group sessions were conducted in the Free State province (where the intervention was to be implemented) from December 2001 to July 2002. Participants in each group included nurse practitioners and doctors working in PHC, provincial tuberculosis coordinators, and clinical managers. Participants were chosen according to their rank (tuberculosis nurse coordinators), and/or level of involvement in patient care (nurses and doctors working in primary care), and/or their level of contact and training with nurses (nurse managers and trainers). Nurses and doctors working in primary care who had a wide range of experience in working in rural and urban areas were chosen.[8] These criteria were communicated to provincial and local tuberculosis coordinators who chose the participants prior to the focus groups. This sampling technique was employed to ensure diversity of experience and opinions thereby minimising the potential for bias. Due to traveling constraints, most chosen participants worked in urban clinics, but at the time of the interviews many had previously working in rural clinics. The Free State province is however considered to be a rural province, and therefore most of the data are representative of conditions in these areas.

Nurses and doctors were interviewed separately to reduce the potential threat of intimidation resulting from hierarchical differences that may arise between the two groups. Verbal consent from each member was obtained for their contributions to be recorded on audio or video-tape, and each participant's confidentiality and anonymity was ensured. For each focus groups session, two observers made hand-written notes. Interviews were conducted until saturation point was reached. To ensure reliability of the collected data, these were supplemented by the visual or audio recordings when

reviewed. Transcripts were repeatedly read and coded by three independent researchers (RGE, LF, BM), and emerging themes were identified from all the data sources.

5.4.2.1 First focus group discussion

Six medical doctors and 15 nurses attending this one-day meeting which was held at a city hotel in Bloemfontein in the Free State province in December 2001. At the start of the meeting, the objectives, as mentioned above, were presented to the participants and the PAL and PALSA initiatives were introduced. Participants were then divided into two groups (doctors and nurses), and each group was moderated by a facilitator (MOB, BM). Thereafter, the groups reconvened for a plenary session to report back on the group discussions.

Below are the questions asked of the participants:

- To determine problems with managing lung diseases (cough and shortness of breath) in primary care.

  - *What are the most commonly occurring lung problems/diseases in the province?*
  - *What are the problems associated with making an accurate diagnosis of respiratory disease in primary care?*
  - *What are the problems of choosing the most effective respiratory treatment?*
  - *What are the problems with communicating with patients and their compliance to treatment?*
  - *What are the problems with coordination and referrals (between clinics, GPs, district hospitals, etc.)?*
  - *What are the solutions to the above problems?*

- To assess the appropriateness of the PAL guideline

  - *What do you think about these guidelines?*
  - *What format is best? (How do you feel about using a flow chart as a guide to diagnosis and treatment?)*

- *What do you think about the amount of detail (too much/too little)? Where should details be dropped or added?*
- *What parts are not applicable to the Free State?*
- *How can this be made to fit into the existing national tuberculosis guidelines?*

5.4.2.2 Second focus group discussion

The second focus group meeting was held in April 2002 at the University of the Free State Community Health Department. The aims of this meeting were to (1) present the first official draft of the PALSA guideline to assess its layout and flow, content, and local applicability, particularly in respect of the diagnostic and treatment recommendations, and (2) to generate short (key) messages derived from the guidelines and thought by the participants to address key diagnostic or treatment barriers encountered in clinical practice. The draft guideline was presented page-by-page by RGE. During the presentation an opportunity was provided for participants to comment. Comments were recorded by members of the team. Thereafter, the group was divided into two (doctors and nurses), with each group being facilitated by one moderator (EDB, BM). The rest of the team members (RGE, LRF, AB, MFZ, MOB) acted as transcribers or observers. Discussions were followed by a plenary session at which each group provided feedback and presented potential key messages.

Below are the questions asked of the participants:

- General comments on the PALSA guideline

  - *What do you think about the content of the guideline?*
  - *Does it cover all major diseases encountered in the province?*
  - *What do you think of the format, as opposed to the IMCI guidelines?*
  - *Will it be simple to use, and are the algorithms easy to follow?*
  - *Does it have too much or too little information?*
  - *Will nurses be able to execute the instructions suggested in the guideline? i.e. find the guideline easy to follow.*
  - *Does the guideline add more responsibility to the nurses?*
  - *Do the drugs in the guideline also appear in the EDL?*

- *Are drawings/illustrations necessary for inclusion in the guideline?*
- *What are your comments about this page (each page was discussed individually)?*

5.4.2.3 Third focus group discussion

The third focus group was held at the University of Free State's Department of Community Health Department in May 2002. The aims were to present and discuss: (1) a revised draft PALSA guideline (2) the number and type of guideline support materials required, and (2) the proposed implementation and training programme. After briefly presenting the progress in the PALSA guideline development process, the proposed training technique (academic detailing) was presented by MFZ and AB, and a short video detailing this method was shown. Thereafter, followed a general discussion addressing the above aims took place.

Below are the questions asked of the participants:

- Training approach

  - *What do you think of this training technique (educational outreach)?*
  - *How can it be improved?*

- Guideline

  - *What do you think of the PALSA guideline?*
  - *Which materials would be useful in complementing/supporting the guideline?*

5.4.3 Face-to-face interviews

Face-to-face interviews to determine the guideline content for correctness (evidence-based validity), local applicability and conformity with local guidelines were conducted. These were conducted with key stakeholders in national (n=1) and

provincial (Free State) health management (n=1), and with respiratory physician specialists (n=5) in Cape Town, South Africa.

Questions asked during the interviews:

- *What do you think of the PALSA guidelines' layout, content and flow?*
- *Do you think that is applicable to the local setting and local guidelines?*
- *How can it be improved?*

5.5 Printed guideline support materials and training programme development

After the second focus group discussion in April 2002 at which the PALSA guideline was reviewed, group members (RGE, LFR, AB, MFZ) met regularly to develop (1) key messages (2) potential guideline support materials, and (3) the training programme. Support materials are any printed materials that enable the user to understand and retain key guideline recommendations. They should reflect the content of the guideline. Drafts of each were sent to the rest of the guideline development team for comment and were presented for comment at subsequent focus group discussions and at sessions at which the intervention was piloted.

5.5.1 Key message construction

Key messages are vectors of information that contain diagnostic, treatment and/or referral advice and serve as prompts or reminders. Its use is intended to aid information retention and ultimately health professional behavioural change.[9] They address identified, changeable barriers, take the form of short 'catchy' sentences that are easily memorised, and can be printed onto intervention materials. 'Changeable' implies that the barrier can be easily addressed within the policy, physical and financial resource limitations of the health system. Key messages in the PALSA project were based on evidence from published medical literature on the effectiveness of respiratory treatment, referral indicators, validity of signs and symptoms predictive

of individual respiratory diseases and syndromes, and both international and PALSA guidelines, as well as information gained from the qualitative evaluation.

An example of how the key messages were developed is shown in the following example for tuberculosis. Firstly, we identified barriers to tuberculosis care. One such barrier is that in most clinics the diagnosis of tuberculosis is the responsibility of one rather than all nurses because of verticalisation of the tuberculosis programme. Therefore, the overall clinic staff index of suspicion for tuberculosis is not high, and not all nurses are familiar with the recommended diagnostic procedures. The key messages therefore provide clear instructions on when to suspect tuberculosis and the appropriate action that must follow. These key messages are presented in the chapter that follows.

5.5.2 Printed support materials

The guideline development team met regularly to discuss which materials would best serve to support the guideline. After initial brainstorming and consideration of the outcomes of the qualitative research the group agreed to develop a desk blotter that could be kept on the nurse's desk in the clinic, and a flip chart that would contain a variety of different scenarios and which would serve as the main educational material during the nurse-led educational outreach session to the local clinic. A pen with one of three key messages printed on its side was also designed. After a series of meetings, the first draft of the desk blotter was conceived and compiled by LRF. Thereafter, it underwent a series of revisions. Only the guidelines, desk blotters and pens were provided to the nurses in the clinics.

5.5.3 Educational Outreach

Academic detailing - non-commercial, short, face to face, in-service interactive educational sessions by a trusted and trained outsider (also known as educational outreach) is an effective strategy for changing practice among physicians.[10 11] Well trained educators visit healthcare professionals to provide evidence-based information

on a specific subject in a concise and objective way through the use of key messages. The educator often provides reminders, pamphlets and/or other educational materials. In PALSA, the primary aim of this intervention strategy is to improve the nurse's adherence to the guideline recommendations and its support materials, and to promote the application and understanding of the key messages. A script was developed based on the materials developed, and served to 'tie' them all together. Nurses (tuberculosis programme coordinators) were chosen to implement the intervention. AB took the lead on designing the training programme with input from an experienced educator in adult education techniques. The guideline development group participated in the conceptualization of the training.

5.6 Piloting the PALSA guideline intervention strategy

The intervention was piloted in three separate sessions. The first session (n=3) was held at a community health centre in an urban area in Cape Town in July 2002. It was attended by 3 clinic staff members who were invited to attend by the facility manager. The aims were to further test and refine the guideline, materials, and implementation strategy. This session was led by AB, and was observed by RGE, LRF, and MFZ. The next two sessions were attended by 4 participants each. Both were held at a community health centre in Thaba Nchu, in the Free State; were conducted on the same day by the same facilitator (LRF); and were held in succession. The intervention was presented as it was intended to be used in the clinics. Feedback was obtained regarding the training concept, and its content, duration, and relevance, as well as potential obstacles to its usefulness. After each pilot session, the development team met to discuss the training and the participants' feedback.

Questions asked of the participants of the pilot sessions:

- *What is your general feeling about the PALSA training?*
- *What are your comments on:*
  - *Time allocated for the training session*
  - *Venue for the training*
  - *Content of the training materials: the guideline, the deskblotter*

- *Relevance of the training on your daily work*
- *The facilitator(s)*

- *What are your general recommendations to the PALSA researchers and FS Provincial Health Authorities on respiratory health care delivery in the province?*

5.7 Ethics approval

Ethics approval for the study was granted by both the University of Cape Town and the University of Free State research ethics committees, and by the provincial departments of both these cities. Oral informed consent was obtained from all qualitative research participants, and their anonymity and confidentiality were ensured. Each participant was informed that participation was voluntary.

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Chapter 6 : RESULTS: DEVELOPMENT OF THE PALSA GUIDELINE

6.1 Outline of chapter

This chapter presents details of the sequence and timing of study activities, the composition of the guideline development group, results of the review of policies, guidelines and the medical literature, and the analysis of barriers to respiratory care in South Africa which led to the process of guideline development through a series of interviews and working groups. Feedback on the PAL guideline and recommendations for its revision will also be discussed. Finally, it describes the completed PALSA guideline and the accompanying support materials for educating nurses in its use.

6.2 Time frame of the PALSA guideline development

The PALSA guideline was developed over a period of two years starting in 2001. Although the development process is presented sequentially, each phase of development did not occur in isolation. Table 22 illustrates the time frames for the different guideline development processes.

Table 22: Time frames of the guideline development process*

Guideline development phase	2001	2002				2003		
	Sept-Dec	Jan-Mar	Apr-Jun	Jul-Sep	Oct-Dec	Jan-Mar	Apr-Jun	Jul-Sep
Review of PAL guideline								
Review of policies, guidelines, and literature.								
Brainstorming								
Focus group discussions								
Face-to-face interviews								
PALSA Guideline development								
Development of materials and training								
Pilot of PALSA intervention								
Motivation for prescribing changes in intervention clinics								

*Adapted from a time frame flowchart presented in Flottorp et al[1]

6.3 The multidisciplinary guideline development group

6.3.1 Composition of the guideline development group

The core guideline development group comprised a specialist respiratory physician (EDB), a clinical epidemiologist with health economics experience (MOB), a public health researcher with a special interest in evidence-based medicine and health systems research (MFZ), 2 physicians with tertiary, secondary and primary health care experience (RGE, LRF), a public health research fellow (BM), and a pharmacist experienced in designing and implementing projects aimed at changing professional practice (AB).

6.3.2 Roles of the guideline development group members

The lead developer (RGE) was responsible for retrieving, synthesising, and presenting evidence from literature or from national policies in draft versions of the guideline. The latter were reviewed and discussed by the rest of the guideline development group. EDB and MFZ helped to review the evidence and develop the guideline. LRF, AB, BM, and MOB provided feedback on the draft versions of the guideline. RGE, LRF, AB, and MFZ participated in the development and piloting of the support intervention materials. All members were involved in the qualitative research discussion groups, and in developing the implementation strategy.

6.3.3 Group decision-making

Where evidence in support of diagnostic or treatment recommendations was lacking or inconclusive, or recommendations were considered by the team to be unsuitable for the practice setting, they were adapted through a process of discussion resulting in informal consensus within the group. All aspects of the guideline were considered in this way.

6.4 Results of review of policy documents, guidelines, and medical literature

6.4.1 Review of local policies and programmes

The policies and programmes that provide the framework for primary health care in South Africa include the following: the National Health Plan,[2] the White Paper on the Transformation of the Healthcare System[3] the Primary Health Care Package[4] the Norms and Standards for primary health care and clinics in South Africa,[5] the National Drug Policy,[6] the Nursing Act,[7] in particular Sections 38A that specify the qualifications and limits of prescribing by nurses. These were considered in detail during the PALSA guideline development process.

6.4.2 Review of guidelines

Local and international respiratory guidelines relating to the diagnosis and management of respiratory conditions were assessed for content, local applicability, level of evidence and grading of recommendations (where included) and presentation. Table 23 lists the more prominent local and international guidelines reviewed. Of particular importance were the South African Essential Drugs List and Standard Treatment Guidelines and the handbook of the South African National Tuberculosis Control.

Table 23: Local and international guidelines reviewed during the PALSA guideline development process.

International guidelines	Local guidelines
• Global Initiative for Asthma[8]	• South African Thoracic Guidelines for Asthma[16]
• Global Obstructive Lung Disease[9]	• South African Thoracic Guidelines for COPD[17]
• ARIA[10]	• South African National Tuberculosis Guidelines[18]
• IUATLD asthma guideline[11]	• Essential Drugs List and Standard Treatment Guidelines[19]
• British Thoracic Society Asthma guidelines[12]	
• Scottish Intercollegiate Guidelines Network guidelines[13]	
• National Institute for Clinical Excellence[14]	
• New Zealand Guidelines Network[15]	

6.4.3 Review of literature

Because the PALSA guideline's content framework was narrow the search for evidence was relatively well-defined. Each diagnostic, drug and non-drug treatment recommendation was critically reviewed in the light of the available evidence. Appendix 3 lists the Cochrane reviews consulted.

6.5 Results of the barriers research

Review of barriers to the provision of quality services for respiratory diseases in primary care led to the following observations which were derived from the results of the qualitative evaluation. Because of the similarities in the derived themes, the data from the various qualitative methods will be presented together.

6.5.1 Knowledge and skills barriers

Both nurses and doctors agreed that nurses received too little training (undergraduate or in-service) in physiology, pathology, and diagnostic procedures to fully understand the scientific basis for many guideline recommendations. The presence of more than one disease in patients led to confusion about which treatments to prescribe. One doctor stated that *"Sometimes health workers, especially nurses show ignorance, uncertainty and reluctance to get involved too much and prefer to refer patients even when there is no need to."* Nurses felt confident about treating, although not necessarily diagnosing, smear-positive tuberculosis, but lacked the skills required to diagnose other respiratory conditions when the sputum results were negative. The doctors and nurses reported that nurses did not know the value of administering medications such as oral prednisone for patients with acute exacerbations, and that they were allowed to prescribe cotrimoxazole to HIV patients.

6.5.2 Difficulties in using guidelines

Doctors commented that *"Nurses are ignorant about guidelines"*. In contrast, nurses expressed dissatisfaction at the large number of guidelines and management protocols, and inconsistent recommendations between them. Limited knowledge about the existence, use and structure of guidelines were mentioned by both groups. Doctors felt that nurses were not able to use disease-based treatment guidelines like the EDL, and said that nurses tended to use symptom-based algorithms mechanistically and with little clinical judgment. This was reflected in statements like *"They [nurses] lack the necessary knowledge and skills to adhere to guidelines."* Nurses on the other hand

reported that they were accustomed to using algorithms such as the tuberculosis diagnostic algorithm in clinical practice.

Nurses were frustrated by the lack of logical flow in some of the guidelines and strongly supported the concept of a simplified guideline. They commented that *"These guidelines [the draft PALSA guideline] are rather more direct. If a patient presents with a lung problem, you can treat promptly. You wouldn't mess up because they are easier to use, nicely tabulated and separation of conditions makes it easier to follow. Clear when to refer, when to prescribe antibiotics, what to give..."*. And *"These guidelines are the same as the EDL, just that they are better designed and have more information. They integrate other conditions such as TB."* The absence of guidelines in some facilities, theft of materials, and non-adherence were commonly cited as additional reasons for poor diagnostic performance and ineffective treatment of patients. The reported limitations of the EDL was that it could not make multiple diagnoses, and assumed that the patients' diagnoses were known on presentation, or that all nurses were sufficiently skilled to make respiratory diagnoses.

6.5.3 Professional barriers: Relationships and status of nurses within the health service.

Nurses expressed frustration with physicians working within the public or private sectors who did not follow TB diagnostic protocols *("Doctors are using ESR readings to make a diagnosis [of tuberculosis]")*, and failed to write referral letters explaining methods used to diagnose tuberculosis. *"In most cases doctors tend to mistake severe chest pains for pleural pains resulting in them diagnosing pulmonary tuberculosis instead of pleural effusion. This can create serious problems in most cases."* Nurses were responsible for notification and documentation of cases and had to therefore explain irregularities to their managers.

Nurses also reported being stressed by their relationships and communication with managers, their patients, and physicians who diagnose TB. They felt disempowered by managers who were autocratic and did not communicate effectively. One nurse cited a problem of a community tuberculosis awareness campaign, launched without

their knowledge. *"Awareness campaigns normally result in an influx of TB patients in clinics, a situation which is sometimes not budgeted for and can result in shortage or compromise on routine medication."*

6.5.4 Organisational barriers

Increased workload from overcrowded clinics left nurses feeling disempowered, frustrated and burnt out. *"Work overload is another contributing factor. How can a doctor or nurse be expected to see more than two hundred patients per day and still be expected to do a good job?"* Others reported that due to poor planning and prioritisation, nurses were required to attend off-site meetings when their colleagues were on leave, leaving clinics understaffed. Most clinics were equipped with the necessary diagnostic equipment and drugs, a finding that was supported by the national health facilities survey at the time.[20] However, in discussion it was learned that not all facilities had supplies of oxygen, nor were they stocked with the full range of medications required in terms of the EDL for primary care.

6.5.5 Patient barriers

Nurses felt demoralised by factors such as poverty and migratory work practices that prevented patients from accessing regular care and adhering to treatment. This perception was supported by statements such as "*We also need to consider the patients' economic status. You will find that a patient is not able to take medication properly because of poverty and hunger. TB medication requires one to eat nutritious food, which they cannot afford.*", and *"The urban-rural migration of patients also contribute significantly to defaulting and/or non-compliance ... by patients."* Other contributory factors were perceived to be patients' cultural beliefs, fear of the stigmatisation of TB and HIV, and denial of the consequences of their high-risk behavior which compromised the care that nurses wanted to provide. *"A lot of TB patients and their relatives still regard TB as witchcraft; they [the patients] are normally referred to us at terminal stages."*

6.6 Feedback on the PAL guideline and recommendations for its adaptation

The feedback and recommendations obtained from the various categories of respondents for adapting the PAL approach and guideline for the Free State province were broadly similar. In the section that follows feedback on the PAL guideline concept, its layout and flow, its content, and recommendations emerging from the qualitative research for its revision are presented.

6.6.1 The PAL concept:

Integrated approach. Integration of tuberculosis with other respiratory diseases was very well received. Reasons cited by nurses for welcoming an integrated approach were that they often felt ill-equipped to manage patients who presented with common symptoms such as cough and shortness of breath; and that they were not always sure how to manage patients who continued to have respiratory symptoms when they had exhausted their diagnostic routine (including bacteriological testing) for tuberculosis. Conversely, other nurses felt ill-equipped to manage tuberculosis patients as their training in tuberculosis management was deficient because of the verticalisation of the tuberculosis control programme.

Syndromic diagnosis and management. The use of symptom and signs to guide the user to make syndromic diagnoses was strongly supported by all. Nurses required a syndromic approach to correct the deficiency in their diagnostic skills – skills that are assumed at the entry point to most disease-specific guidelines. The PAL guideline also often assumed availability of diagnostic aids like chest radiographs or spirometry.

Feedback on the layout and flow of the PAL guideline. Respondents liked the algorithmic or flowchart format, but felt strongly that it needed to be simplified. Comments on the layout and flow mainly related to the first page of the PAL guideline which, in the first focus group session, was reported to be an obstacle both for nurses and doctors being able to proceed to subsequent pages. These comments are discussed in the section that follows. Pages 4 to 6 of the PAL guideline which deals with the initial management of the patient are presented in Appendix 2.

Links between sections on the first page of the PAL guideline were not clear. Links between the sections *Ask, Look, Listen and Classify* on page 4 of the guideline were not clear (Appendix 2). For example, the questions are not presented in a sequence that corresponds to a standard approach to a patient (namely, personal details, presenting complaints, past medical history, comorbid illnesses, etc.). Another example is that most of the information relating to the symptoms and signs in these sections are presented in the form of a question, but the relevance of each question and their relation to the action step that follows is not always evident or explained. For example, the third question in the *Ask* section assesses whether chest pain, if present, is new or severe. Neither of these terms are qualified. Yet, severe pain is a symptom of *severe pneumonia or very severe disease,* and pleuritic chest pain is a symptom of *pneumonia*. The duration of the pain (whether it is new or not) is not used as a 'sign' in the *Classify* section.

Another example relates to difficult breathing (the second question of the *Ask* section) (Appendix 2, page 4). After establishing the presence of this symptom (which is not defined), it is not clear how the question relates to the *Classify* section. Furthermore, in the *Ask* section, further breathlessness questions are asked. Again, the link between these questions and the disease in question (asthma) is not made explicit. To establish this link requires background knowledge about these diseases, or a very good understanding of the guideline. While some of these difficulties can be attributed to the fact that the PAL guideline is intended for use by primary care physicians and nurses, the lack of flow was considered to make it cumbersome and difficult to follow.

Use of the 'signs' in the 'Classify' section of page one of the guideline to diagnose the disease syndromes was not clear (Appendix 2, page 4). A comment was that the section *Classify* contained a heading which read *Signs*, yet symptoms were included in that section. Another comment from the guideline development group was that the *Classify* section did not easily encourage or facilitate making more than one diagnosis, which considering the frequent presence of co-morbidity in patients with respiratory disease (usually a chronic one), was considered by the group to be a serious omission.

Failure to establish an explicit link between the acute and chronic sections. The PAL guide does not clearly distinguish between acute and chronic disease presentations. For the chronic respiratory diseases, there is no explicit link between the acute and chronic sections that assists the user to consider asthma or COPD. This tends to perpetuate the view that these diseases cannot or need not receive the same emphasis as acute disease. It also perpetuates the perception that the only, or most useful function of primary care, is to identify and treat acute disease. Instead, the guideline presents these diseases separately in the 'chronic' section of the guideline. On the first page, patients assessed as having chronic disease are to be referred to the district hospital for assessment.

The dosages of medications were often presented in a separate section. To determine the treatment steps and dosages for each disease the user has to refer to a different section to obtain treatment information. No instructions are provided on which section and on which page the corresponding treatment is located. For the management of severe wheezing (Appendix 2, page 6) the user had to refer to the *Treatments* section in another part of the guideline (not included as part of appendices of this thesis).

6.6.2 Content of the PAL guideline

Disease mix. An obvious advantage of PAL is that the choice of diseases can be customised to a country's needs. For example, malaria which is not endemic to the Free State province of South Africa, did not have to be included.

Knowledge, skills and scope of practice requirements of the PAL guideline user. Most functions required of the healthcare worker using the PAL guideline fell within the scope of local nurse practices, except for detailed auscultation, and use of and interpretation of spirometry. However, the PAL recommendations were not fully compatible with the South African National Tuberculosis Control Programme, and the Essential Drugs List (EDL).

6.6.3 Recommendations for local adaptation of the PAL guideline

Recommendations for the layout and flow of the PAL guideline. It was recommended that the guideline should be as short as possible, and contain essential diagnostic prompts linked to action steps. The layout of the document should be simple and easy to follow – simple enough to eventually commit to memory through frequent use. Users required a guideline that was durable and could be kept on hand in the clinic room to guide their consultations. It was also clear that relevance to their clinical practice setting and ownership (through being consulted during its development) were important to users.

Recommendations to improve the first (entry) page of the PAL guideline. Although the *Ask, Look Listen* approach had a logical appeal, these placed the emphasis on technique rather than on problem-solving. The latter was better served, especially for nurses, by providing a route map with simpler prompts that led to a syndromic diagnosis which in turn was integrated with treatment recommendations.

6.6.4 Suggestions for local adaptation of the PAL guideline

Separation of acute from chronic disease using a two or three week rule. Use of a two or three week rule to make an early distinction between acute and chronic presentations was suggested. Although this approach has disadvantages, it is useful firstly for identifying those that require acute care, but also draws attention to the presence of chronic disease and the need to consider tuberculosis in patients with all forms of chronic respiratory presentations. In PAL, disease is only considered under the heading "if known COPD", or if the symptoms have been present for more than 3 weeks (Appendix 2, page 4).

Assessment of patients with acute disease according to levels of disease severity. To ensure early recognition, treatment and referral of severe patients, the link between suggestive symptoms and signs and disease severity was to be tabulated. This assessment was to form the first step in the evaluation of acute disease.

Pneumonia versus lower respiratory tract infection. The term pneumonia was to be replaced by lower respiratory tract infection as pneumonia can only be confidently diagnosed with the aid of a chest radiograph, which is not available in many if not most first level facilities. Syndromic management of lower respiratory tract infections was to include possible pneumonia and bronchitis associated with sputum production and/or colour change.

The re-classification of asthma into levels of control rather than categories of severity. The guideline development group felt that in accordance with the emerging trends in asthma management at the time (which have recently become more prominent),[21 22] instead of basing treatment on the level of assessed asthma severity, treatment was to be control-driven. That is, the emphasis was to be on determining the level of control as the basis for initiating, increasing or decreasing asthma treatment, as would be the case in treating hypertension to achieve a target level of blood pressure.

The role of spirometry in COPD and asthma. The role of spirometry in primary care for the diagnosis and management of COPD remains controversial.[23] However, the guideline development team felt that inclusion of spirometry in the guideline would be a barrier to the diagnosis of asthma or COPD as lung function equipment is not available at this level. Instead it was suggested that information gleaned from history-taking be used to diagnose each condition. It was felt that the guideline should provide for referral to the next level of care of those requiring further evaluation.

The need to consider tuberculosis in all patients with respiratory disease could receive more prominence. Since one of the main purposes of PAL is to increase case detection of tuberculosis, it was thought that prompts to consider tuberculosis could appear more prominently in the PALSA guideline. This should appear at every decision node, including the management of acute disease.

Tailor the HIV and AIDS sections to the local context. It was advised that HIV and AIDS staging be included, together with HIV and AIDS screening questions, and instructions to offer VCT.

6.7 Feedback on the PALSA guideline and recommendations for its revision

In the section that follows feedback on the layout, and flow, and the content of the PALSA guideline will be presented, and then the PALSA guideline will be described in detail. The PALSA guideline is presented in Appendix 5.

6.7.1 Feedback on the draft PALSA guidelines

Layout and flow of PALSA guideline. The nurses who reviewed the PALSA guideline were unanimous that it was user-friendly, simple, and more direct than most primary care guidelines. It was felt that most nurses, regardless of qualification, would be able to follow the algorithms. Diagnostic and treatment steps were clearly presented without ambiguity. One participant stated that it was *"clear when to refer, when to prescribe antibiotics, what to give, like IMCI"*. Another stated, *"These are easy to follow, even a lay person could use them"*. The use of colour and graphics were welcomed and added to its appeal. Incorporation of management steps into one section of the flow chart, as opposed to a number of related sections also simplified the guideline considerably.

Overall content of the PALSA guideline. In terms of content, the nurses appreciated the integration of tuberculosis diagnosis and management with that of other respiratory tract conditions. They agreed that the medications and other treatment recommendations in the guideline were found to be consistent with current practices and available resources.

The following recommendations made by focus group discussion participants were included in the PALSA guideline:

- The entry symptom related to breathing problems changed from 'difficulty breathing', to 'difficulty in breathing', and finally to 'difficult breathing' (Appendix 6, page 1).

- Dosages of inhaled corticosteroids, rather than the number of puffs were included to accommodate differences in the various metered-dose inhaler formulations in use (Appendix 6, page 13).
- The type and dosages of the recommended analgesics were standardised.
- The timing of referrals to doctors after initial diagnosis of asthma and COPD was reduced from three months to one month (Appendix 6, pages 13, 14).
- Colour photographs of oral candidiasis were included as they were considered by the focus group participants to be useful for nurses and to patients as part of patient education (Appendix 6, page 9). Candidiasis was also added as a cause of sore throat as it is common in HIV-infected patients (Appendix 6, page 8).
- VCT was replaced by VCCT (voluntary confidential counselling and testing) at the request of the nurses, an abbreviation not used elsewhere in South Africa (Appendix 6, page 20). Participants indicated that that use of the term VCCT was preferred in the Free State, the emphasis being on 'confidentiality'. At the time of these consultations anti-retrovirals were not available in public sector clinics.

Changes to prescribing provisions requested by respondents. Focus group participants identified negative effects of certain policies and the difficulties of translating them into practice. For examples, nurses were not permitted to initiate, but could dispense repeat prescriptions and change the dosage of inhaled corticosteroids. This disadvantaged patients in rural clinics since it was difficult for them to access clinics with doctors. Consequently, most asthmatics did not receive inhaled corticosteroids. It was proposed that prescribing provisions for nurse practitioners be changed to include initiation of this class of drug. Other suggested changes in prescribing provisions are listed in Table 24. The guideline development group also motivated for circulars to be sent to intervention clinics to re-enforce the prescribing of cotrimoxazole prophylaxis for stages 2, 3 and 4 HIV positive patients.

Table 24: Prescribing changes successfully motivated for by the PALSA guideline development team.

Medications	Previous prescribing regulation	Amended prescribing provision
Inhaled corticosteroids	Nurses were not permitted to initiate inhaled corticosteroids. They were, however, allowed to issue repeat medications, or change the dosage of inhaled corticosteroids.	Nurses were allowed to initiate inhaled corticosteroids.
Oral corticosteroids	Nurses were not permitted to prescribe oral corticosteroids for patients with an acute exacerbation of asthma/COPD as stat dosages or as short courses.	Nurse could prescribe a stat dose and short course for patients with asthma or COPD exacerbations.
Broad-spectrum antibiotics for tuberculosis suspects with negative sputa.	The antibiotic to be prescribed for tuberculosis suspects with 2 negative sputa was not standardised.	Amoxicillin 500mg orally three times a day for five days was standardised to be the drug of choice.

Recommendations made by the national tuberculosis co-ordinator. The national tuberculosis co-ordinator provided feedback and suggested that the cut-off for suspecting tuberculosis be reduced from three to two weeks. This pre-empted a change in national policy that was under discussion at the time. The Free State province became the first to embrace this change.

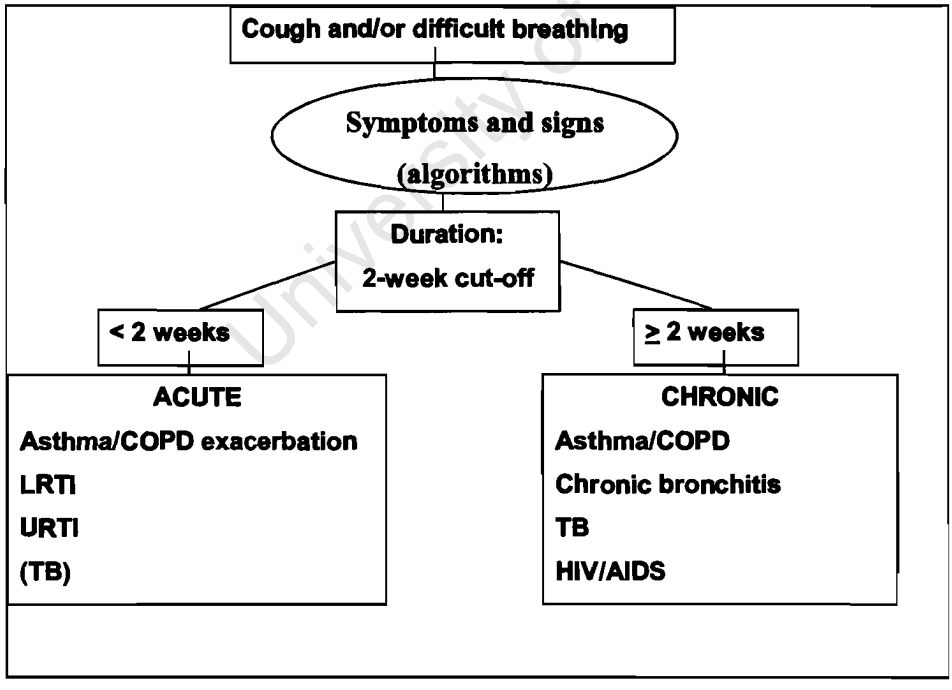
6.8 Description of the PALSA guideline

The PALSA guideline addresses the diagnosis and management of acute asthma and COPD exacerbations, lower and upper respiratory tract infections, asthma, COPD, chronic bronchitis, tuberculosis, the diagnosis and staging of HIV and AIDS, and cotrimoxazole prophylaxis.

6.8.1 Flow and layout of the PALSA guideline

Figure 2 depicts the concept behind the PALSA guideline. This will be discussed in more detail below.

Figure 2: Figure illustrating flow of PALSA guideline



Entry point to the PALSA guideline. An outline of the flow of the PALSA guideline is presented in Figure 2, and the guideline is presented in Appendix 5. Cough and/or difficult breathing serve as the entry point into the guideline. Difficult breathing is defined as the presence of breathlessness at rest or on activity, wheezing and/or tight chest.

Acute versus chronic presentations. If symptoms are new or worsening, or there is uncertainty about the underlying respiratory diagnosis, then the duration of the main presenting symptoms is elicited. A two-week cut-off distinguishes acute from chronic disease (Figure 2; Appendix 5, page 6). A diagnosis of stable chronic disease is assumed in patients who report no worsening of symptoms, and/or no uncertainty regarding the underlying diagnosis. The guideline was also intentionally designed to make both acute and chronic diagnoses at the same visit in each patient. For example, a diagnosis of an acute exacerbation can be made in a patient who has underlying poorly-controlled asthma or COPD. The guideline is also designed to make more than one diagnosis, for example, community-acquired pneumonia in addition to pulmonary tuberculosis (Appendix 5, page 5.).

6.8.2 Acute conditions in the PALSA guideline

Determining disease severity. Patients with acute presentations are assessed using the disease severity table (Appendix 5, page 2.) By assessing the degree of breathlessness, mental state, use of breathing (accessory) muscles, breath rate, heart rate, and haemoptysis the presentation is assessed as being either severe, moderate, or mild. The purpose of this table is to ensure that patients requiring urgent assessment, treatment, and/or referral are identified as early as possible and managed appropriately.

Acute exacerbation of asthma or COPD. Patients with respiratory complaints for 2 weeks or less, and whose symptoms are considered to be severe and are associated with wheezing or tight chest, are diagnosed and treated as having an exacerbation of asthma or COPD (Appendix 5, page 2). In the PALSA guideline no distinction is

made between asthma and COPD exacerbations as it is often difficult to distinguish clinically between the two conditions, and because the recommended initial management of these conditions in the EDL is the same. If the acute exacerbation is assessed as *severe*, initial management by a nurse is to position the patient for ease of breathing; administer 40% face-mask oxygen, or oxygen at 4 L/min via nasal cannulae; to call for an ambulance, refer to a doctor; administer $beta_2$-agonist from an MDI via spacer or by nebulisation; and to give a stat dose of oral prednisone (Appendix 5, page 4). *Moderate or mild exacerbations* are treated with $beta_2$-agonist therapy (via spacer of nebuliser) administered every 20 minutes for one hour, and with a stat dose of oral prednisone. After one hour, the patients' condition is re-assessed. If no change, beta-agonist therapy is repeated and the patients are re-assessed within one hour. If worse, subsequent management is the same as for a severe exacerbation. If better or asymptomatic, the patients may be discharged. The discharge plan ensures that compliance and inhaler technique is acceptable and that appropriate medications are prescribed with instructions to return if the there is no continuing improvement. It includes provision for a follow-up visit to confirm the diagnosis of underlying obstructive airways disease, and patients are encouraged to stop smoking, and criteria are provided to prompt patients to return if there is no clinical improvement.

Lower respiratory tract infections. In patients with respiratory symptoms for less than 2 weeks and evidence of severe respiratory distress on examination, the presence of a temperature of greater than or equal to 38 degrees Celsius categorises the condition as a severe LRTI (Appendix 5, page 2). Patients with mild or no symptoms are assessed as having either an obstructive lung disease exacerbation or LRTI (or tuberculosis, suppurative lung disease, or upper respiratory tract infection), depending on the associated symptoms (Appendix 5, page 5). Patients are further categorised as being at high or low risk of a severe LRTI. The former includes patients with co-morbid disease such as diabetes and HIV infection or AIDS. These receive immediate antibiotics and are referred to the next level facility, while patients at low risk are treated at home. The guideline directs that patients with symptoms of LRTI be considered for tests for HIV infection and tuberculosis.

Upper respiratory tract infections. Patients are assessed as having an upper respiratory tract infection (URTI) if they have respiratory complaints for 2 weeks or less, and the following symptoms: runny nose, sore throat, pain and/or tenderness over sinuses, or an ear problem (Appendix 5, page 6). Although URTIs do not typically present with cough or difficult breathing they constitute a common cause of respiratory symptoms and are therefore included in the guideline. URTIs covered in the guideline are the common cold, pharyngitis, tonsillitis, sinusitis, otitis externa and media. Allergic rhinitis and oral candidiasis are also included.

Rhinitis. A *common cold* is diagnosed in the presence of a mild sore throat and/or fever. Patients are reassured that antibiotics are not necessary. The only EDL and guideline provision for such patients is oxymetazoline (0.05%) nose drops prescribed for no longer than 1 day (Appendix 5, page 7). *Allergic rhinitis* is diagnosed in the presence of sneezing and itching for four weeks or more, on more than 4 days each week (i.e. on most days). 0.9% saline nose drops and chlorpheniramine is prescribed for both conditions, but patients with persistent (symptoms ≥four days a week) are referred to the next level facility for corticosteroid aqueous nasal spray.

Acute sinusitis. *Viral sinusitis* is diagnosed in the presence of a clear nasal discharge, mild pain over sinuses, and/or post-nasal drip. Patients are reassured that antibiotics are not necessary. Treatment options include: bicarbonate of soda or 0.9% saline nasal solution, oxymetazoline nose drops, and/or paracetamol (Appendix 6, page 7). *Bacterial sinusitis* is diagnosed in the presence of symptoms for 7 days or more, severe symptoms regardless of duration, pussy nasal discharge, and/or facial or dental pain and tenderness. Treatment options are the same as for viral sinusitis, but include antibiotic treatment (amoxicillin). Patients are referred to the next level if a tooth abscess is suspected, there is swelling around the eye or facial swelling, and/or failure to respond to medication after 10 days (Appendix 6, page 7).

Acute pharyngitis, tonsillitis, oral candida. A diagnosis of *acute pharyngitis* is made if the throat is reddened but there is no purulent material ("red without pus"). Patients are reassured that an antibiotic is not necessary. Treatment options include salt water mouthwash and paracetamol (Appendix 5, page 8). *Bacterial tonsillitis* is diagnosed when the throat is red and there is pus or white patches on the tonsils or tonsillar area.

Treatment options are the same as for acute pharyngitis, except that antibiotics are included (phenoxymethylpenicillin, or erythromycin if penicillin-allergic patients). Patients are referred if they have marked difficulty swallowing, inability to open mouth (suggesting a quinsy), and/or more than four documented episodes a year warranting referral for assessment for removal of tonsils. *Oral candidiasis* is considered if white patches are present on cheeks, gums, tongue and palate. Treatment includes nystatin lozenges or drops. The nurse is instructed to exclude HIV infection in all such patients. A separate page in the guideline provides photographs of the various appearances of oral candidiasis.

Acute and chronic ear problems. If *skin of the outer ear* is involved, an antibiotic (flucloxacillin, or erythromycin if penicillin-allergic) and paracetamol is prescribed. If there is *ear canal* involvement, then the above-mentioned treatment is also prescribed, but, in addition, the ear is dry mopped. Patients are referred if in addition to the above they are known to have diabetes, or the condition does not respond within two days. *Acute otitis media* is diagnosed if middle-ear pathology is observed or suspected for less than 2 weeks duration. The recommended treatment includes the following: antibiotic (amoxicillin, or erythromycin in penicillin-allergic), paracetamol, and dry mopping of the ear. Patients are to be referred if no response after 5 days, swelling or tenderness of the skin behind the ear, and/or persistent pain. *Chronic otitis media* is diagnosed if pus from the ear is present for two weeks or more. No treatment other than dry mopping and paracetamol is recommended. Patients are referred if there is no improvement after four weeks, a foul-smelling discharge is present, a large hole in the eardrum is observed, hearing loss, and/or pain. Colour pictures of the various ear conditions and instructions on how to dry mop the ear are provided (Appendix 5, page 11).

6.8.3 Chronic conditions in the PALSA guideline

Patients are assessed as having chronic disease if they have respiratory symptoms for two weeks or more or are known to have chronic lung disease. The first objective is to confirm or exclude the presence of asthma or COPD. Other chronic conditions addressed in the guideline are chronic bronchitis, tuberculosis, and HIV and AIDS.

Distinguishing between asthma and COPD. The absence of lung function equipment in primary care facilities and the erratic availability and limited knowledge on the use of peak flow meters by nurses necessitated the use of the syndromic approach to the diagnosis of asthma and COPD and led to the exclusion of peak flow meter readings from the guideline (Appendix 6, page 12). Table 25 lists the symptoms and history questions used to distinguish asthma from COPD. For asthma, the questions related to the age of onset of symptoms, history of atopy, family history of asthma, variability of symptoms, triggers or aggravating factors, and response to bronchodilators. For COPD, the questions related to the onset after the age of 35 years, deterioration of symptoms over time, onset and frequency of breathlessness, and a smoking history of 15 pack years or more.

The guideline instructs the nurse to default to a diagnosis of asthma should diagnostic uncertainty exist. If only one feature of asthma or COPD, no significant history of smoking, but a positive history of hypertension, ischaemic heart disease, and/or diabetes, then a cardiac or non-lung causes of breathlessness is to be considered.

Table 25: Table listing the symptom and history variables used to distinguish asthma from COPD in the PALSA guideline.

Ask if:	Ask if:
• Symptoms started during childhood or early adulthood. • History of hayfever, eczema and/or allergies. • Family history of asthma. • Symptoms only during attacks with periods of normal breathing in between. • Symptoms are usually worse: at night; in the early hours of the morning; during an upper respiratory tract infection or when the weather changes. • Symptoms improve or disappear after using inhaler.	• Symptoms started later in life (usually after the age of 35 years). • Symptoms slowly worsened over a long period of time. • Long history of daily or frequent cough and sputum production (usually starts long before the onset of shortness of breath). • Short of breath for most of the day, rather than at night or during the early hours of the morning. • History of heavy smoking eg. More than 20 cigarettes / day for 15 years or more.

Asthma. The aims of asthma treatment are clearly stated in the guideline (Appendix 6, page 13). This are defined as minimal (ideally no) daytime or nighttime symptoms, minimal or no asthma attacks, minimal need for 'quick relief medications', and no limitation of daily activities. The nurse is also instructed to identify the patient's current level of asthma control by enquiring about the following: day and night time symptoms. Table 26 lists the levels of control as presented in the PALSA guideline. Well-controlled asthma is diagnosed if daytime symptoms are present for less than 2 times per week, and if nocturnal symptoms are reported for less than 2 times per month. Poor control is diagnosed if daytime symptoms are continuous and nocturnal symptoms are reported to be frequent.

Table 26: Table listing the levels of control of asthma as presented in the PALSA guideline.

LEVEL OF CONTROL	WELL-CONTROLLED	MODERATE CONTROL	POOR CONTROL
Daytime symptoms per week	< 2 times / week	2 – 4 times / week	Continuous
Night time symptoms per month	< 2 times / month	2 – 4 times / month	Frequent

Treatment is prescribed according to the level of control (Table 27). If the level of control is good (well-controlled), then the patient uses an inhaled bronchodilator when necessary, and a dosage of 200-400µg inhaled corticosteroids daily. For poorly-controlled asthma, the dosage of inhaled corticosteroid is increased to 800-1600 µg, theophylline is added, and a short-course of oral antibiotics is prescribed. These medications are the only treatments available for asthma in the primary care sector.

Pharmaceutical management is according to a step-up or step-down system, and patients are to be reviewed every three months. If complete control is achieved at the three month visit, then medication is continued and is maintained and the treatment may be stepped-down at the next visit (that is, after 6 months of control). If control is poor, treatment is stepped up, and the nurse should consider adding a short course of oral steroids. The patient is to be re-assessed within one months time.

Table 27: Table listing the treatment options according to the level of asthma control as presented in the PALSA guideline.

LEVELS OF TREATMENT	LOW (if well-controlled)	MODERATE (if moderate control)	MAXIMUM (if poor control)
Inhaled salbutamol	2 puffs when needed	2 puffs when needed	2 puffs when needed. May be required 4-6 times per day.
Inhaled corticosteroids	200-400 micrograms per day	800 micrograms per day	800-1600 micrograms per day
Slow-release theophylline (Doctor to initiate)	-	-	1 tablet twice a day
Oral prednisone	-	-	40mg orally (once daily) for 14 days to gain rapid control.

COPD. The aim of COPD management is to encourage patients to stop smoking, improve symptoms with inhaled bronchodilators, and to recognise and treat acute exacerbations. Table 28 lists the criteria used to diagnose COPD disease severity (Appendix 5, page 14).

Table 28: Table listing criteria used to diagnose disease severity as presented in the PALSA guideline.

	MODERATE	SEVERE	SEVERE COPD WITH COMPLICATIONS	INFECTION
Symptoms	Mild breathlessness on usual activity	Breathlessness on minimal activity or continuously	Ankle oedema	Increased sputum purulence or colour change to yellow/green

Treatment for all disease severity levels included inhale bronchodilators (salbutamol or ipratropium bromide) and theophylline, except for moderate disease. However, antibiotics (amoxicillin, or erythromycin if penicillin-allergic) plus a short course of oral steroids, and diuretics are prescribed for patients assessed as having infection and right heart failure (ankle oedema), respectively.

Table 29: Table listing the treatment options according to the level of COPD severity as presented in the PALSA guideline.

Level of severity	Mild/moderate COPD	Severe COPD	COPD with complications	COPD with infection
Bronchodilators				
Inhaled salbutamol	2 puffs when needed	2 puffs when needed	2 puffs 4 times a day	2 puffs when needed
Inhaled ipratopium bromide	-	2 puffs when needed (up to 4 times per day)	2 puffs 4 times a day	2 puffs when needed (up to 4 times per day)
Theophylline	1 tablet 2 times per day	1 tablet 2 times per day	1 tablet 2 times per day	1 tablet 2 times per day
				Amoxycillin 500mg three times a day for 7 days OR If penicillin-allergic, Erythromycin 500mg four times for 7 days. Prednisone 40mg orally (once daily) for 14 days

Chronic bronchitis. Chronic bronchitis is considered in patients with chronic cough with or without sputum production and no breathlessness (Appendix 5, page 15). The guidelines identifies those at risk of having this condition as heavy smokers, patients with known lung damage, and those exposed to heavy occupational dust or domestic air pollution. Other suggestive features are daily cough with or without sputum production for months or years with onset of symptoms in middle or old age. Treatment includes avoidance of the suspected cause, if any. The guideline advises that patients with these symptoms who do not have a history of smoking be referred for assessment of other forms of lung disease.

Tuberculosis. Increasing the suspicion of tuberculosis among nurses is considered to be one of the main benefits of the guideline. Users are therefore encouraged to suspect tuberculosis at several decision points, regardless of the duration and severity of the symptoms. Tuberculosis is suspected in the presence of the following: cough for two weeks or more, unintentional weight loss, loss of appetite, night sweats and fever, haemoptysis, and in known HIV or AIDS patients (Appendix 5, page 16). Additional instructions are provided on the timing and choice of investigations, and/or referral to a higher level of care for other diseases and provision for follow up is made. Instructions are provided on how to collect sputum, how to investigate the tuberculosis suspect, and an treatment recommendations.

HIV and AIDS. Page 20 of Appendix 5 lists the features suggestive of HIV infection or AIDS. The guideline provides a brief description of VCCT, follow-up of HIV positive patients, co-trimoxazole prophylaxis; and WHO staging (Appendix 5, pages 20-22).

6.9 Description of the support materials and educational outreach methods

Although not the primary focus of this thesis, providing a description of the intervention support materials and their development is vital in understanding how the guideline informed their development, and how they informed the development of the guideline. Providing a description also serves to increase the understanding of the reasons for conducting such comprehensive research during the development of the

guideline. However, detailed descriptions and discussions on each component are beyond the scope of this thesis. The final support materials are presented in Appendices 6 to 7. Appendix 13 details how the interventions relate to one another and the barriers each one addresses.

Selection of key messages. The PALSA key messages can be classified into 4 categories (Appendix 13): (1) directives in words – phrases that contain a diagnostic or treatment recommendation (2) visuals – cartoon-like visual prompts which give instructions or serve a reminders (3) questions – a phrase asking the user about a diagnostic or treatment recommendation, usually starts with "Did you know?" (4) gimmicks (treatment wheels) – special aids that serve to simplify the management decision process. The key messages included on the pens for the nurses were:

- Cough ≥ 2 weeks → think TB
- Inhaled steroids control asthma
- HIV+ & symptomatic → cotrimoxazole for healthy life

Printed support materials. Based on the outcomes of the focus group discussions, the intervention development team agreed to include a desk blotter (Appendix 6) and flip chart (Appendix 7) as part of the printed support materials. Other materials were a pen with the key messages printed on the side, a placebo inhaled corticosteroid metered-dose inhaler (for demonstration of correct technique), a commercial spacer, and a spacer constructed from a plastic bottle used for soft-drinks.

Desk blotter. A colour A3-sized, laminated desktop blotter containing graphics and consisting of 5 panels was developed (Appendix 6). Each panel addressed specific disease diagnoses and/or management strategies identified from the focus groups, to be areas of knowledge gaps,. The key messages were incorporated into the desk blotter. The blotter was to be used by the nurse as a quick-reference tool and for patient education. In Appendix 13 the information included in the desk blotter has been tabulated and linked to their corresponding key messages and source barriers.

Flipchart. The flipchart was designed for use by nurse trainers and was intended to be the focus of the educational outreach sessions (Appendix 7). This A3-sized freestanding booklet consisted of 7 pages and served as a stimulus for discussion around specific disease or management scenarios, and for introduction of the key messages (Figure 1). The first few pages allowed for discussion on recognising severe and non-severe disease, with specific emphasis on recognizing and treating the seriously ill respiratory patient. The last few pages dealt with the diagnosis and management of non-severe respiratory disease and smoking cessation. The discussion points are detailed in the script that accompanies the materials during the educational outreach sessions (Appendix 8).

Educational outreach. The educational outreach training aimed for combining the content of the guideline and materials using the key messages with reflective, experiential learning, role-play, and non-judgemental feedback. A detailed description of the educational outreach methods will be reported elsewhere.[24]

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Chapter 7 : METHODS AND MATERIALS: Validation Study

7.1 Aim of the PALSA Validation Study

The primary aim of the PALSA validation study was to test the diagnostic accuracy of the PALSA guideline by comparing the diagnoses made by a primary nurse care practitioner using the guideline with those made by a respiratory physician who had access to special investigations like chest radiography and spirometry. A secondary aim was to determine which symptoms and signs best predicted respiratory disease amongst the study participants because of the paucity of medical research to support the use of syndromic algorithms in the South African primary care settings, and to establish whether the PALSA diagnostic algorithms needed to be refined accordingly.

7.2 Study design

The validation study was a prospective cross-sectional study with consecutive recruitment of patients presenting to a primary health care centre with respiratory symptoms. The study took place between November 2002 and December 2003, and was planned and coordinated by RGE, who also served as the lead study investigator.

7.3 Study population

Eligible patients were identified by the study nurse from among those presenting to the triage nurse in the waiting room of the study site by asking, "Do you have a cough and/or difficulty breathing?" Those 15 years and older who responded positively were eligible for inclusion unless they refused to participate or provide written consent, were known to have severe psychiatric problems or required urgent care.

7.4 Study site

The Retreat Community Health Center, a local primary healthcare facility, was chosen as the study site. This facility provides a 24-hour accident and emergency service, as well as an outpatient clinic that operates on weekdays only. It services seven middle- to low income suburbs and about 9000 patients are seen at the clinic each month. Twenty percent of these patients are seen in the Accident and Emergency Unit. Patients of all ages are seen at the clinic except neonates and pregnant women. The Centre provides services in radiology, community psychiatry and social work, and has a pharmacy. A full-time voluntary HIV and AIDS counselling and testing service is also offered to patients. Emergency services are contacted telephonically in the event of an emergency requiring transport to the local district hospital. Patients who present to the clinic for an acute complaint are triaged immediately by nurses and are sent the emergency department. The rest are attended to in the outpatient department of the clinic after presenting to the triage room. A limited set of investigations are permitted at this level. Bloods and sputa for tuberculosis testing are sent to a local laboratory. Lung function testing is not available at this level of care.

7.5 Assessment of subjects by the PALSA Nurse

One nurse (SN) with over 20 years of nursing experience in a variety of clinical settings including primary care was the designated study nurse. Her duties were to recruit patients, obtain consent, and make 'PALSA' diagnoses using the guideline for each patient enrolled in the study. Each morning she screened patients as they arrived at the clinic for unscheduled or scheduled (follow up) appointments, and collected their clinic folders. Consecutive patients, 15 years or older, who answered 'yes' to the screening question were considered to be eligible to participate in the study. On occasion, patients were referred directly to the study nurse by the emergency unit. clinic doctor or nurse because they were deemed suitable for inclusion.

After obtaining consent the nurse entered the patient details onto a screening log and took a brief history as required by the PALSA guideline. A copy of the consent forms can be viewed in Appendix 9. She then measured and recorded the height, weight, blood pressure, temperature, pulse, respiratory rate and oxygen saturation for each patient (Appendix 10). Enrolment of patients for the study took place between 07H30 and 16H00 during weekdays only. Using the PALSA guideline she could make up to 3 diagnoses. The list of PALSA diagnoses can be found in Table 30. She was instructed not to deviate from the algorithms as presented in the guideline, nor to record diagnoses based on her clinical experience. Instead she was to rigidly apply the answers to the algorithms, and record the 'guideline' diagnosis. This was done to ensure that the diagnoses as suggested by the guideline were accurately reflected in the final results. Thereafter, all patients were sent to the radiology department for a postero-anterior chest radiograph. She was blinded to the results of the radiographs and the assessments made by the primary care and respiratory physicians.

Table 30: PALSA diagnostic categories

Acute mild/moderate COPD/asthma exacerbation
Acute severe COPD/asthma exacerbation
Asthma - moderate
Asthma - severe
Asthma - well-controlled
COPD - complications
COPD - infective exacerbation
COPD - moderate
COPD - severe
Chronic bronchitis
Common cold
Acute otitis media
Chronic otitis media
Outer ear furuncle
LRTI - high-risk
LRTI - low-risk
Intermittent allergic rhinitis
Persistent allergic rhinitis
Bacterial sinusitis
Viral sinusitis
Oral candida
Pharyngitis
Bacterial tonsillitis
Suspected TB
Non-PALSA diagnosis

7.6 Assessment of patients by a primary care physicians

After the nurse's assessment was completed, patients were seen by one of two primary care physicians (RGE, TvR) who were blinded to the nurse and respiratory physician diagnoses. Both primary care physicians each had over 6 years postgraduate clinical experience. The physicians took a comprehensive standardised medical history and performed a physical examination that included all systems relevant to the

guideline and any other medical conditions present. This information was recorded in duplicate onto a structured record form. One copy of the record form was left in the patients' folders, and the other copy with the exception of the page containing the primary care physicians' diagnoses were filed for the respiratory physician to review. A copy of the structured record form used is provided in Appendix 11. The physicians performed flow volume loops before and after inhalation of 400μg of salbutamol administered from a pressurised metered dose inhaler, using a PM1 Spirometer (Erich Jaeger®, Germany). Training of the physicians to perform these manoevres were undertaken by a qualified respiratory technologist over a period of one week prior to starting the study.

The primary care physicians systematically recorded the patients' clinical details, the results of spirometry and chest radiography. Their diagnoses were made without the assistance of the PALSA guideline. The results of these and the chest radiograph of each patient were reviewed by the physician, and if considered necessary, additional investigations (sputum, blood or other tests) were requested. They recorded their levels of confidence in each diagnosis made, using a 5-point Likert scale (1 representing the lowest level of confidence, and 5 the highest level of confidence or certainty). In all subjects in whom even a low level of suspicion of tuberculosis was recorded, sputum specimens for examination and culture were obtained. In accordance with the South African National Tuberculosis Control Programme,[1] sputum was only obtained for examination for tuberculosis in patients who were suspected to be infected. Thus, not all patients had their sputa tested. In most instances, the first sputum was taken at the study visit, and a second on the following day. Details of the algorithm followed by the respiratory physician, which is the same as that adhered to by the South African National Tuberculosis Control Programme can be found on page 16 of Appendix 6. More details of the methods used to test for and examine the sputa will be discussed later.

Further patient management was performed according to usual clinic procedures and standards of care. Up to four guideline diagnoses could be made in each patient. Patients requiring referral or further care were sent to one of the following: the medical officer at the clinic, to a district hospital or specialist clinic in the local academic hospital, or to the local tuberculosis clinic. No laboratory results were

available to the study physicians at the initial visit, but a follow-up visit was arranged for those requiring further follow-up, discussion of results, or investigation (for example, after a trial of therapy). Patients requiring respiratory specialist attention or in whom the respiratory diagnoses was uncertain were referred to the respiratory clinic at the local academic hospital.

7.7 Assessment of patients by a respiratory physician

Two qualified respiratory physicians (RD, AH), who were both blinded to the nurse and primary care physicians' diagnoses independently reviewed each patient's data. This evaluation was done off-site and patients were not present. They had access to the structured record sheets containing information regarding the presenting complaints, history and examination findings, as well as chest radiograph films and printouts of the lung functions, but not their diagnoses. They could record up to four diagnoses for each patient onto a structured record sheet. Diagnoses were accorded a PALSA diagnosis and if none applied they were assigned to the 'non-PALSA diagnosis' category (Table 30).

The GINA and GOLD guideline parameters were adhered to for diagnoses of asthma or COPD, respectively. These parameters, however, merely acted as diagnostic guides, as their final diagnoses were informed by their clinical judgment based on clinical information and investigations. For example, the assessment of levels of control of asthma was informed by spirometric results, but the final assessment was based on clinical judgment taking history and examination into account. A PALSA diagnosis of mild/moderate COPD was based on GOLD stages 2-3, and severe COPD on stage 4 COPD. High-risk LRTI was assessed according to the likelihood of mortality according to age, concomitant disease and disease severity. Low-risk LRTI were diagnosed in patients who could be treated as outpatients, or those who in the opinion of the respiratory physician did not require antibiotics.

Severe acute exacerbations included patients who required urgent treatment and/or needed to be referred for further management. Mild/moderate exacerbations included patients who according to their symptoms or history required immediate but not

necessarily urgent treatment, and/or in the opinion of the respiratory physician could be managed in the clinic.

7.8 Investigations

7.8.1 Chest radiography

A postero-anterior x-ray film was taken at the clinic's radiography department. A Shimadzu x-ray machine was used and films were developed immediately in the Kodak processor. X-rays were repeated if the quality was not thought to be acceptable to the radiographer or the doctor. The films were then taken directly to the primary care physician by the patient for assessment.

7.8.2 Spirometry

All lung function tests were performed on one of three Jaeger PM2 spirometers (Fredrich Jaeger, Germany). This apparatus employs a digital gas volume sensor for bi-directional measurements of airflow enabling performance of flow volume loops. The PM2 sensor was cleaned and disinfected once a week as recommended by the manufacturer. Calibration was performed daily using a 3-Litre calibration pump, and disposable mouthpiece incorporating a microbiological filter was used for each patient. All lung function tests were performed daily between the hours of 08H00 and 16H00. Patients were asked to refrain from smoking, drinking hot or cold beverages and from using an inhaled bronchodilator prior to testing, where possible. However, it was not possible to ensure that all subjects withheld bronchodilator therapy for four hours prior to testing. Therefore some values were potentially 'post-bronchodilator'. The majority were not.

Forced expiratory manoevres were performed with the patient seated with a nose clip on her/his nose. In accordance with American Thoracic Society recommendations these were repeated until 3 satisfactory expiratory flow volume curves had been obtained. The PM2 quality-assurance steps provide prompts when curves are satisfactory and do not permit the next step until the requisite curves are obtained.

Four hundred micrograms of inhaled salbutamol was then administered via a metered dose inhaler using a Volumatic® spacer device. A post-bronchodilator blow was performed ten to fifteen minutes later. FEV1, FVC, and FEV1/FVC ratio were presented in liters and percent of predicted. Reversibility readings were presented in milliliters and percentage. The study doctor reviewed the results immediately, and a copy of the test was placed into the study file for review by the specialist.

7.8.3 Blood pressure measurement

Blood pressure was measured using the COLIN Press-Mate Advantage® apparatus that measured blood pressure non-invasively and automatically and recorded it in units of mmHG. The appropriate cuff size for the patient's arm width was placed around the upper arm. The measurement was displayed on the monitor and the result was automatically printed along with the oxygen saturation result. The manufacturer's instructions for use of this apparatus were adhered to throughout the study.

7.8.4 Pulse oximetry

Oxygen saturation was measured using the COLIN Press-Mate Advantage® apparatus and recorded as a percentage. A non-invasive Dura-Sensor DS-100®, which is a reusable finger probe for adults weighing over 40kg was used. The measurement was displayed on the monitor and printed out along with the blood pressure result. The manufacturer's instructions for use of this machine were adhered to throughout the study.

7.8.5 Temperature

The temperature (in degrees Celcius) was measured using a glass-mercury thermometer placed under the tongue for at least 3 minutes. The patients were instructed to not drink any warm or cold fluids before this measurement.

7.8.6 Heart Rate

The heart rate (beats per minute) was measured manually. The exact number of radial pulse beats in 60 seconds was measured.

7.8.7 Respiratory Rate

The respiratory rate (breaths per minute) was measured by counting the number of breaths taken by the patient in 60 seconds.

7.8.8 Sputum collection

A first specimen was collected immediately and a second specimen the following day. Instructions were provided to patients on how to optimally produce sputa (Appendix 5, page 16). At the clinic, the smears were refrigerated, and later transported to the laboratory on the same day that it was collected to ensure viability of the sputa. The sodium citrate method was used to process the smears which were stained using the Ziehl-Nielsen method and then examined for acid fast bacilli (AFB) by one reader. A positive smear was reported if at least one AFB was visible per 100 immersion fields. Sputa were cultured on a slope of Löwenstein-Jensen medium and incubated at 37°C for about six weeks. Bacteriological confirmation of tuberculosis was accepted if two sputum smears collected on different days were positive as reported above, or one culture was positive with or without a positive smear.

7.9 Statistical Analysis

7.9.1 General analysis

After data collection, data were entered and cleaned by 5 data capturers. Each entry was double-checked by RGE to ensure correct capture. Where missing data related to information retrieved from history, an independent person reviewed the nurse's handwritten notes to determine whether she had recorded the data. Where the data related to information that could be easily obtained from the patient and that was unlikely to have changed significantly from the time the study was conducted, an attempt was made to contact the patient to obtain the information. Data were analysed using Stata 8® statistical software.

Descriptive analysis was conducted to describe the data distributions, to examine outliers, and to determine whether parametric or non-parametric methods should be applied to subsequent univariable analysis. Inter-physician agreement was measured by determining the kappa statistic. Interpretation is as follows: 0-0.20 means slight agreement, 0.21-0.40 means fair agreement, 0.41-0.60 means moderate agreements, 0.61-0.80 means substantial agreement, and 0.81-1.00 means 'almost perfect agreement".[2]

7.9.2 Sample size determination

Prevalence of PALSA conditions among patients with cough and/or difficult breathing at Retreat Day Hospital as diagnosed by an experienced generalist (December 1999, Summer season) is shown in Table 31 and Table 32.

Table 31: Estimates of prevalence of respiratory diseases likely to be encountered in the study.

Chronic Obstructive Pulmonary Disease	31%
Upper Respiratory Tract Infections	25%
Asthma	24%
Lower Respiratory Tract Infections	9%
Suspected Tuberculosis	8%
Tuberculosis	3%

Table 32 lists the proposed prevalence distributions of the PALSA diagnoses.

Table 32: Likely prevalence distributions of the PALSA diagnoses

ACUTE	
Severe	
Acute obstructive lung disease	8%
Lower respiratory tract infections	4%
Moderate	
Mild obstructive lung disease	10%
Lower respiratory tract infection	5%
CHRONIC	
Chronic obstructive pulmonary disease	
Moderate	4%
Severe / complications	8%
Infections	5%
Asthma	
Well-controlled	4%
Moderate	8%
Severe	4%
Chronic bronchitis	4%
Tuberculosis	11%
Upper respiratory tract infections	
Sore throat	9%
Runny nose	9%
Sinuses	3%
Ear problems	4%
TOTAL	100%

The sample size of 2000 was intended to provide reasonably precise estimates of sensitivity, specificity, positive and negative predictive values, for a range of key diagnoses (Appendix 4). For example, for a relatively rare diagnosis such as tuberculosis, which has a predicted prevalence of 3% in this setting, if the sensitivity of a nurse using PALSA to diagnose tuberculosis, compared to a specialist, was 70% then the corresponding 95% confidence intervals was predicted to be 58-82%. The sample size of 2000 was said to provide reasonable estimates of chance – corrected agreement between PALSA doctor and the specialist expressed as a kappa statistic (Appendix 14). For example, for a condition with 4% prevalence and a kappa value of 10%, the 95% confidence interval for the kappa will be 5-15%. For a prevalence of 15% and a kappa of 60%, the 95% CI for kappa will be 55-65%.

7.9.3 Analytic methods to determine diagnostic accuracy of the guideline

Studies determining the diagnostic accuracy of tests, compare the results of one or more tests with a reference standard.[3] The sensitivity, specificity, positive and negative predictive values, areas under receiver operating characteristic curves, and positive and negative likelihood ratios for each index test compared with each reference standard (respiratory physician diagnoses) were calculated. 95% confidence intervals (CI) for proportions were calculated based on binomial distributions. 95% confidence intervals for areas under receiver operating characteristic curves were also determined. These were calculated for broad disease categories (asthma, COPD, exacerbations, LRTI, URTI) and levels of diseases severity or control diagnosed by the nurse and were compared with those diagnosed by the respiratory physician, except for diagnoses of suspected and confirmed tuberculosis where the primary reference standard was considered to be the primary care physician.

The nurse and physicians were allowed to make three and four diagnoses per patient, respectively, as it was estimated that these were potentially the most number of concurrent diagnoses made in one consultation when (1) using the guideline (nurse) (2) considering concurrent respiratory and comorbid diagnoses (physicians). Thus, when analysing the false positive and negative results we analysed each potential diagnostic category. We wanted to have a more accurate reflection of concurrent

disease presentations. For the nurse using the guideline the primary diagnosis was defined as the first diagnosis that the guideline 'led' the nurse to. This does not mean that the secondary of tertiary diagnoses were less important. For the specialist, the primary diagnoses was the condition that he/she thought to be the reason for the presentation. Any additional or comorbid conditions were recorded as secondary, tertiary, or quartenary diagnoses.

7.9.4 Analytic methods to derive predictors for each disease

Continuous measurements (pack-years, heart rate, respiratory rate) were categorised according to the PALSA guideline criteria, and according to cut-points obtained from published literature or from noting obvious inflection points on receiver operating characteristic (ROC) curves. The relationships between each diagnostic element and the reference standard diagnosis were tested using chi-square or Fischer's exact tests, depending on distribution of data. Data for each question included in the structured record sheet were examined for a relationship with each outcome. Categorical variables were also reduced to single items and each one was examined independently by univariable analysis.

Criteria for including a variable into the reduced multivariable model was a risk ratio (RR) of > 2.0 or less than 0.5, with a sample size of more than 100, and p-values of less than 0.05. However, variables not showing significance, but which were thought to be important in multivariate analysis were included. As far as possible we adhered to the rule of including at least 10 outcome events for each independent variable included in the model to reduce overfitting of data.[4] Stepwise multiple regression analysis was performed using the Spiegelhalter Knill-Jones[5] technique to determine which combination of symptoms and signs best predicted each disease Variables were excluded from the models if not independently associated with the reference standard, and if their odds ratios were less than 0.5 and more than 2, aiming for a parsimonious model of powerful predictors. Independent (mutually-adjusted) associations between each predictor and the reference standard diagnosis were then expressed as likelihood ratios instead of odds ratios. This entailed adjusting crude likelihood ratios with shrinkage factors obtained by logistic regression for potential confounding by other

related variables, as described by Spiegelhalter and Knill-Jones[5]. The adjusted likelihood ratios of different predictors can be multiplied by each other because they are independent. Confidence intervals for adjusted likelihood ratios were estimated by non-parametric bootstrapping of logistic regressions, with 2000 replications, and using the bias-corrected percentile method.

This analysis was conducted for each disease, except URTI, as the number of patients with respiratory physician diagnoses of this condition was too small. For asthma and COPD, 3 separate analyses were performed to reflect clinical practice and to inform future guideline revisions. The categories were for patients: (1) ≥15 years (2) ≥15 years with respiratory physician diagnoses of obstructive lung disease (asthma or COPD) (3) ≥40 years with respiratory physician diagnoses of obstructive lung disease (asthma or COPD). Only for tuberculosis was the primary care physicians' diagnoses used as the reference standard.

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Chapter 8 : RESULTS OF THE VALIDATION STUDY

8.1 Overview of the chapter

This chapter presents the results of the assessment of diagnostic accuracy of the PALSA guideline for asthma, chronic obstructive pulmonary disease (COPD), acute exacerbations, tuberculosis, and lower and respiratory tract (LRTI) disease. The following will be considered.

- The accuracy of the guideline as used by the nurse in diagnosing conditions included in the PALSA guideline using the respiratory physicians' diagnoses as the reference standard. For tuberculosis, the nurse's diagnosis of suspected tuberculosis will also be compared to the primary care physicians' assessment of suspected and bacteriologically-proven tuberculosis.

- How frequently and which conditions were misclassified by the nurse using the guideline by examining the false positive and false negative diagnoses, thereby determining the diagnostic and treatment implications of the nurse making an incorrect disease classification.

- Which symptoms and signs best predict each condition in patients with cough or difficult breathing, by estimating their crude and adjusted likelihood ratios, respectively. For asthma and COPD, to estimate these separately for the following patient subgroups: (1) all patients (≥ 15 years) (2) patients ≥ 15 years with obstructive lung disease (asthma or COPD) (3) patients ≥ 40 years with obstructive lung disease.

8.2 Patient characteristics

8.2.1 Patient sample

Of the 1400 patients enrolled into the study a total of 1392 were eligible for analysis. A flow-diagram illustrating the flow of patients in the study according to the Standards for Reporting of Diagnostic Accuracy[1] (STARD) is presented in Figure 3. Reasons for exclusion were as follows: 6 absconded, 1 was screened twice and 1 was unable to give an adequate history.

Figure 3: Disposition of study subjects (STARD diagram).

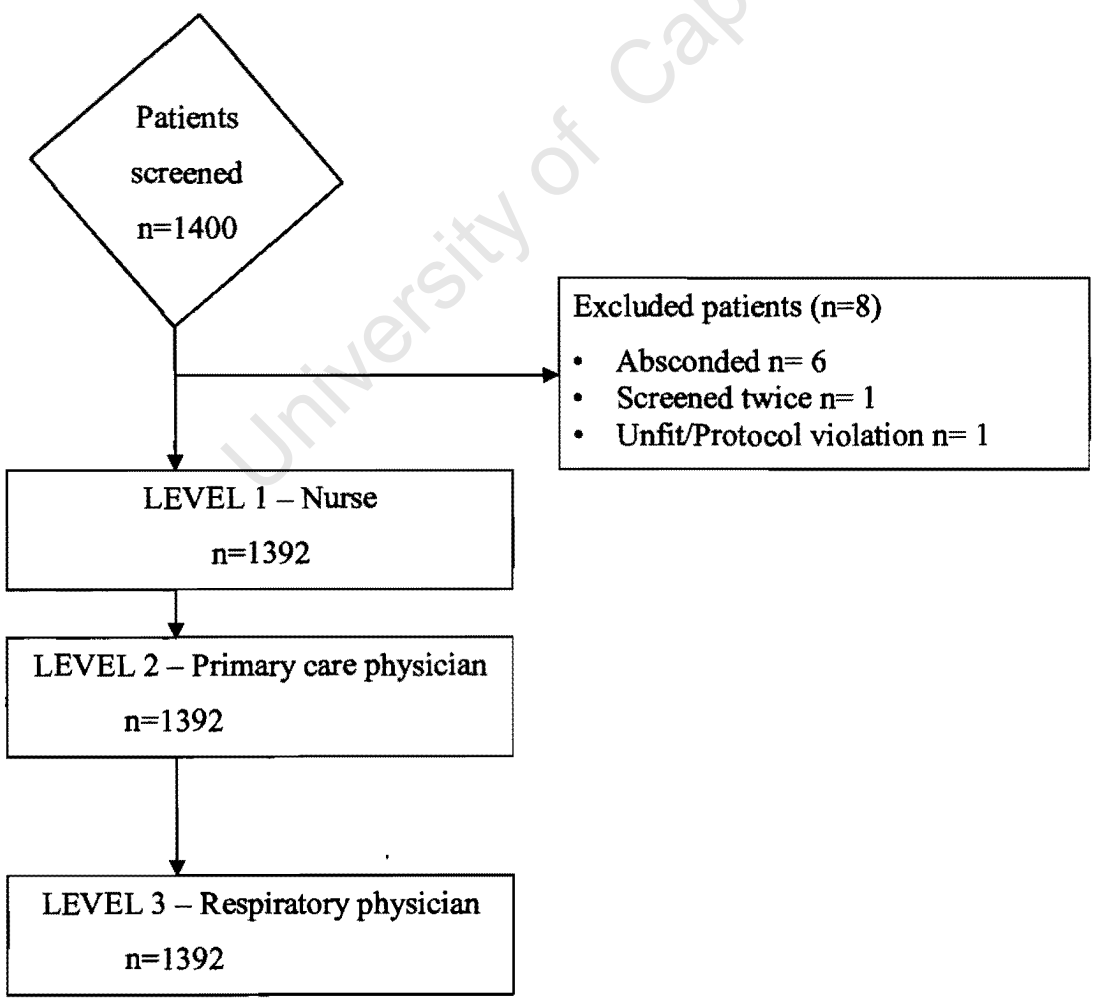


Table 33 lists the patient characteristics of the study population. There was a predominance of females (63%), the median age (range) was 48 years, and 806 (58%) were between the ages of 30 and 60 years.

Table 33: Age and sex distribution of study population.

Variable	n = 1392
Age	
Mean age (SD), years	48 (±16)
Age categories, n (%)	
15-29 years	215 (15)
30-60 years	806 (58)
>60 years	371 (27)
Sex, n (%)	
Females	876 (63)
Males	516 (37)

8.2.2 Presenting symptoms

The symptoms resulting in patients' inclusion in the study were cough and difficult breathing (in 71%), cough alone (in 19%) and difficult breathing alone in 10% (Table 34) Tight chest (50%), wheeze (45%), and sputum production (35%) were the most commonly reported additional symptoms, whereas symptoms of upper respiratory tract infection were a less common presentation in this study.

Table 34: Relative frequency of cough or difficulty breathing in patients entered into the validation study (n=1392).

Screening question	Number (%)
Cough and difficult breathing	986 (71)
Cough alone	264 (19)
Difficult breathing alone	142 (10)
Tight chest	690 (50)
Wheeze	630 (45)
Sputum	490 (35)
Night sweats	180(13)
Weight loss	163 (12)
Increased sputum production	129 (9)
Runny nose	121 (8)
Pleuritic pain	102 (7)
Sneeze/itchy nose	54 (4)
Haemoptysis	53 (4)
Blocked nose	50 (4)
Fever	43 (3)
Sore throat	35 (3)
Sinus pain	12 (1)
Discharge from ear	8 (1)
Painful ear	6 (0.4)
Hearing loss	1 (0.07)
Tooth pain	1 (0.07)

8.2.3 Previous respiratory conditions

More than two-thirds (69%) of patients reported a previous diagnosis of one or more associated respiratory or related disease (Table 35). Asthma (43%) was the most commonly reported respiratory disease, followed by COPD (20%) and TB (15%). Data detailing the medications that each patient used at the time of the study is not provided in this analysis.

Table 35: History of previous respiratory and related diagnoses in the study population (n=1392)*.

Disease	Number (% of total population)
Asthma	592 (43)
COPD	281 (20)
Previous tuberculosis	202 (15)
Previous lung surgery	13 (1.0)
Bronchiectasis	7 (0.5)
Chronic bronchitis	5 (0.5)
Current tuberculosis	2 (0.1)
Pulmonary embolism	2 (0.1)
Interstitial lung disease	2 (0.1)
Lung Cancer	1 (0.1)
Cardiopulmonary lung disease	1 (0.1)

* Some reported more than one previous respiratory diagnosis. For each disease the denominator is 1392.

8.2.4 Previous non-respiratory medical conditions

Table 36 lists the past medical conditions reported on presentation. Cardiovascular disease, including hypertension was present in 38%; allergies, including allergic rhinitis in 16%; and metabolic conditions, including diabetes mellitus in 10%.

Table 36: History of non-respiratory medical conditions in patients in the validation study (n=1392).*

Medical condition	Number (% of total population)
Cardiovascular	523 (38)
Allergies	225 (16)
Metabolic	144 (10)
Neurological	60 (4)
Gastrointestinal	31 (2)
Gynaecological	21 (2)
Haematology	5 (0.4)

* Some patients reported more than one previous medical condition. For each disease the denominator is 1392.

8.2.5 Smoking history

The prevalence of a history of smoking (current or former) was high. Just over three-quarters (76%) of the population had a history of smoking, and the majority (47%) reported ongoing tobacco use (Table 37). Seventeen percent of patients admitted to having previously used cannabis, with 92% reporting its use for years.

Table 37: Smoking status of the study population.

Smoking status (n = 1390)#	**Number (% of total population)**
Never smoked	330 (24)
Ex-smoker	407 (29)
Current smoker	653 (47)
Smoking history (pack-years) (n = 1386)*	
<20	930 (67)
20-39	277 (20)
>40	179 (13)
Duration of cannabis use (n = 237)	
Days	3 (2)
Weeks	1 (1)
Months	10 (5)
Years	182 (92)

Data on smoking status unavailable for 2 patients
* Data on smoking history unavailable for 6 patients

8.2.6 Spirometry

The mean spirometric values are presented in

Table **38**. For the first 19 patients, the data for spirometric testing were lost due to a technical error. For 25 patients, ATS criteria were not met. The mean FEV1 was 66% predicted and the mean FVC was 75% predicted. The mean FEV1/FVC ratio was 87% and the mean number of patients with a change in FEV1 of ≥15% and ≥200mL after bronchodilator testing were 30%.

Table 38: Spirometric values of the study sample (n=1348).

Spirometry values	
FEV1 (% predicted), mean (95% CI)	66 (65-67)
FVC (% predicted), mean (95% CI)	75 (74-76)
FEV1/FVC ratio (%), mean (95% CI)	87 (86-88)
Reversibility,† (%) mean (95% CI)	11 (10-12)
Number of patients with reversibility,‡ n (%)	424 (30)
Airflow limitation, n (%)	
FEV1/FVC ratio <70%	918 (66)
FEV1 < 80% (% predicted), mean (95% CI)	312 (23)

† ΔFEV1 ≥ 15% only
‡ ΔFEV1 ≥ 15% and ≥ 200mL

Table 39 lists the mean FEV1 and FEV1/FVC ratios for each disease category as diagnosed by the respiratory physician.

Table 39: Spirometric values for each disease category.

Disease classification	No.	Mean FEV1 (% predicted; 95% CI)	Mean FEV1/FVC ratio (%; 95% CI)
Asthma	489	62 (60-64)	81 (79-82)
Well-controlled	49	78 (70-87)	92 (89-96)
Moderately controlled	180	65 (61-68)	84 (81-86)
Poorly-controlled	260	57 (55-60)	76 (74-79)
COPD	353	45 (43-47)	69 (67-72)
Mild/moderate COPD	225	56 (53-58)	77 (74-79)
Severe COPD	107	26 (25-28)	57 (53-60)
COPD with complications	21	24 (20-27)	54 (46-62)
Acute exacerbation	287	54 (51-56)	76 (74-78)
Severe exacerbation	90	42 (38-46)	71 (67-76)
Mild/moderate exacerbation	197	59 (56-62)	78 (75-81)

8.2.7 Respiratory diagnoses made by the nurse using the guideline

The most common diagnoses made by the nurse using the guideline were asthma (38%), followed by suspected tuberculosis (37%), COPD (29%), and acute exacerbations (26%). URTI was diagnosed in only 7% of patients (Table 40).

Table 40: Respiratory diagnoses made by the nurse using the guideline (n=1392).*

Nurse (guideline) diagnoses	Number (%)
Asthma	533 (38)
Suspected tuberculosis	516 (37)
Chronic obstructive pulmonary disease	404 (29)
Acute exacerbation of asthma/COPD	363 (26)
Lower respiratory tract infection	160 (11)
Chronic bronchitis	53 (9)
Upper respiratory tract infection	98 (7)
Allergic rhinitis	9 (0.7)

* Up to 3 diagnoses per patient

8.2.8 Respiratory diagnoses made by the respiratory physician.

The respiratory diagnoses made by the respiratory physicians are listed in Table 41. Asthma was the most prevalent condition (36%), followed by COPD (27%), acute exacerbation (21%), and LRTI (20%). Tuberculosis was suspected in 19% of patients. These served as the reference standard against which the diagnostic accuracy of the nurse using the PALSA guideline was judged.

Table 41: Respiratory diagnoses made by the respiratory physician (n=1392).*

Respiratory physician diagnoses	Number (%)
Asthma	508 (36)
Chronic obstructive pulmonary disease	381 (27)
Acute exacerbation of asthma/COPD	293 (21)
Lower respiratory tract infection	283 (20)
Suspected tuberculosis	260 (19)
Allergic rhinitis	245 (17)
Cardiovascular disease, including hypertension	224 (16)
Other lung conditions	211 (15)
Metabolic diseases (including diabetes mellitus)	159 (11)
Chronic bronchitis	66 (5)
Upper respiratory tract infection	40 (3)

* Up to 4 diagnoses per patient

8.2.9 Inter-observer agreement between the respiratory physicians

Table 42 illustrates the agreement between the respiratory physicians for 200 patients. Agreement between the physicians for all conditions were satisfactory. Kappa values for asthma, COPD and acute exacerbations ranged from 0.66-0.70. For suspected tuberculosis and LRTI, these values were less satisfactory (0.57).

Table 42: Levels of agreement between the respiratory physician diagnoses (n=200).

Respiratory physicians diagnosis	Agreement, %	Expected agreement, %	Kappa	Standard Error
Asthma	85	51	0.70	0.09
COPD	84	53	0.66	0.09
Acute exacerbations	88	61	0.70	0.09
Suspected TB	85	65	0.57	0.09
LRTI	85	65	0.57	0.09

8.3 Asthma

8.3.1 Accuracy of the nurse using the guideline in diagnosing asthma

Table 43 lists the diagnostic accuracy of the guideline in the hands of the nurse in diagnosing asthma (n=533), using the respiratory physicians' diagnoses (n=508) as the reference standard. More than three-quarters of patients were correctly diagnosed by the guideline (sensitivity 77%). The guideline's performance was good with an accuracy, defined as the area under the receiver operating characteristics curve (ARUC), of 0.81 (Figure 4). The positive likelihood ratio value indicates that a nurse using the guideline was 4.83 times more likely to make a correct diagnosis in patients who are also thought to have, as opposed to those thought to not have, asthma by the respiratory physician.

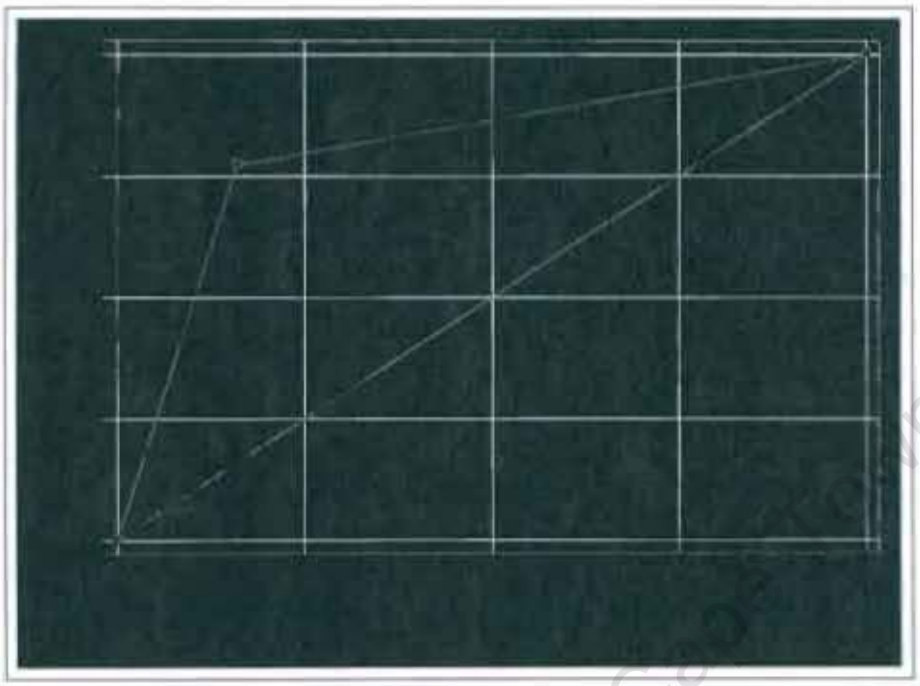
Table 43: Diagnostic accuracy of the nurse using the PALSA guideline in diagnosing asthma with respiratory physicians' diagnosis as the reference standard.*

True positive, n	392
True negative, n	744
False positive, n	140
False negative, n	116
Sensitivity, % (95% CI)	77 (73-81)
Specificity, % (95% CI)	84 (81-86)
PPV, % (95% CI)	74 (70-77)
NPV, % (95% CI)	87 (84-89)
LR+	4.83
LR-	0.27
ARUC (95% CI)	0.81 (0.78-0.83)

PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-: negative likelihood ratio, ARUC: area under the receiver operating characteristics curve.

* Nurse diagnoses (n=533). Respiratory physician diagnoses (n=508)

Figure 4: Accuracy of nurse using the guideline using the respiratory as the reference standard.



8.3.1.1 False positive diagnoses of asthma

Overall, 26% (100%-PPV) of patients thought by the nurse to have asthma had another condition. These are listed in Table 44. COPD was diagnosed as the primary diagnosis in 11% (16), LRTI in 29% (40), cardiovascular disease in 15% (21), and other lung conditions in 17% (24) patients. COPD was diagnosed as additional diagnoses in 9 cases, yielding a total of 25 COPD diagnoses.

Table 44: False positive diagnoses for the diagnosis of asthma.

Diagnostic categories	Primary respiratory physician diagnoses, n (%)	Additional COPD diagnoses made as secondary, tertiary, or quaternary diagnoses by the specialist,* n
LRTI	40 (29)	1
Other lung conditions	24 (17)	2
Cardiovascular	21 (15)	1
COPD	16 (11)†	
Acute exacerbation	10 (7)	4
Chronic bronchitis	7 (5)	
Allergic rhinitis	7 (5)	
TBS	5 (3)	1
Metabolic	4 (3)	
Viral sinusitis	1 (0.7)	
Common cold	2 (14)	
ENT	1 (0.7)	
Infective	1 (0.7)	
Rheumatology	1 (0.7)	
Total	140 (100)	9

* The specialist physician could make a maximum of four diagnoses per patient.
† For the total number of COPD diagnoses, add the COPD additional diagnoses made by the specialist as secondary, tertiary or quaternary diagnoses (n=9).

8.3.1.2 False negative diagnoses of asthma

Fourteen percent (100%-NPV) with respiratory physician diagnoses of asthma were missed by the nurse. Of these, COPD was diagnosed in 66% (35 (30%) as primary and 42 (36%) with additional diagnoses) (Table 45). In addition, 32% (37) were diagnosed as having acute exacerbations, and 24% (28) were suspected of having TB. The nurse using the guideline missed 23% (FP=116) of the asthma cases. Of these, 30% (35) were diagnosed with COPD. Although, a further 32% (37) of patients were diagnosed with acute exacerbations, 62% (23) of these were also diagnosed by the nurse as having COPD as either the secondary, tertiary, or quaternary diagnoses.

Table 45 False negative diagnoses for the diagnosis of asthma.

Diagnostic categories	Primary nurse diagnoses, n (%)	Additional (secondary or tertiary) COPD diagnoses made by the nurse*, (n)
Acute exacerbation	37 (32)	23
COPD	35 (30)†	
TBS	28 (24)	17
Chronic bronchitis	5 (4)	
LRTI	5 (4)	
NP	5 (4)	
Common cold	2 (2)	2
Total	116 (100)	42

* The nurse could make a maximum of three diagnoses per patient.
† For the total number of COPD diagnoses, add the additional COPD diagnoses made by the nurse (n=42) to the total number of primary diagnoses (n=35).

8.3.2 Accuracy of the guideline in determining levels of asthma control

In order to determine how many patients would receive the correct asthma treatment from the nurse using the guideline, given their level of asthma control as assessed by the respiratory physician, we compared the nurse diagnoses (well-, moderately-, or poorly-controlled asthma) to that of the respiratory physicians'. Results show that despite the excellent performance of the guideline to detect asthma as a syndrome without lung function testing (Table 43), it does not perform as well at classifying levels of asthma control based on symptoms and signs alone (Table 46). For well-controlled asthma, the guideline's sensitivity was 32%, the specificity was 93%, the likelihood ratio was 4.72, and the area and under the ROC was 0.63. Values for moderately-controlled disease were similar. The guideline performed best at identifying poorly-controlled disease with a sensitivity of 58% specificity of 87%, and area under the ROC curve of 0.72.

Table 46 Distribution of diagnoses for each level of asthma disease control (n=1392).

Levels of control	Well-controlled	Moderately-controlled	Poorly-controlled
True positives, n	18	49	154
True negatives, n	1245	1132	979
False positives, n	91	74	147
False negatives, n	38	137	112
Sensitivity, % (95% CI)	32 (20-46)	27 (20-33)	58 (52-64)
Specificity, % (95% CI)	93 (92-94)	94 92-95)	87 (85-89)
PPV, % (95% CI)	17 (10-25)	40 (31-49)	51 (45-57)
NPV, % (95% CI)	97 (96-98)	89 (87-91)	90 (88-91)
LR +	4.72	4.29	4.43
LR -	0.78	0.78	0.48
ARUC (95% CI)	0.63 (0.56-0.69)	0.60 (0.57-0.63)	0.72 (0.69-0.76)

PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-: negative likelihood ratio, ARUC: area under the receiver operating characteristics curve.

8.3.3 Prevalence of clinical examination features in patients with asthma

Table 47 shows the prevalences of symptoms in patients diagnosed with asthma. Difficult breathing (94%), cough (91%), response to bronchodilator (88%), and a previous diagnosis of asthma (85%) were most prevalent. Most (55%) patients reported between 1 and 5 exacerbations per year. Nine percent of patients also report a previous diagnosis of COPD. Most patients (70%) reported a smoking history, but only 20% smoked for more than 20 pack years.

Table 47: Frequency distribution of history and examination features in patients with asthma (n=508).

Variables	Patients with specialist diagnosis, n (%)
Difficult breathing of any duration	478 (94)
Cough of any duration	460 (91)
Response to a bronchodilator	447 (88)
History of asthma	432 (85)
Day to day variability	432 (85)
Seasonal variability	417 (82)
Symptoms triggered by the weather	376 (74)
Female	375 (74)
Daytime shortness of breath	346 (68)
Symptoms triggered by environment stimuli	319 (63)
Nocturnal tightness of chest	313 (62)
Family history of asthma	303 (60)
Daily cough	302 (59)
Daily or frequent cough	297 (58)
Nocturnal shortness of breath	298 (59)
Daytime tightness of chest	289 (57)
Difficult breath ≥ 2 weeks	286 (56)
Nocturnal cough	282 (56)
Wheeze on auscultation	281 (55)
Nocturnal wheeze	278 (55)
Cough ≥ 2 weeks	266 (52)
Symptoms triggered by respiratory tract infections	263 (52)
Daytime wheeze	247 (49)
Symptoms triggered by emotion	221 (44)
Daily or frequent sputum production	205 (40)
History of hayfever	203 (40)
Symptoms slowly worsened over time	130 (26)
Short of breath for most of the day	109 (21)
Known allergies	102 (20)
Cough and sputum production preceded the onset shortness of breath	93 (18)
Symptoms triggered by exposure to allergies	78 (15)
Dagga use	62 (12)
Never used a bronchodilator before	46 (9)
History of COPD	45 (9)
Crepitations	23 (5)
Number of exacerbations per year	
1-5 per year	271 (55)
≥5 per year	100 (20)
None	126 (25)
Smoking history	
Never	150 (30)
Former	144 (28)
Current	214 (42)
≥20 pack years	100 (20)

8.3.4 Analysis of history and examination predictors of asthma

8.3.4.1 Predictors of asthma: ≥ 15 years

8.3.4.1.1 Univariable analysis of predictors of asthma: ≥15 years

Table 48 lists the significant univariable predictors of asthma in patients ≥ 15 years as measured by their crude likelihood ratios. In this age category: onset of symptoms before the age of 20 years (LR+ 6.28), a previous diagnosis of asthma (LR+ 5.79), allergies (LR+ 5.08), seasonal variation of symptoms (LR+ 5.13), day-to-day variability of symptoms (LR+ 4.34), triggering of symptoms by emotions (LR+ 4.05), respiratory tract infections (LR+ 3.16) or environmental factors (LR+ 3.16) were most predictive. Daytime wheezing (LR+ 3.65) and chest tightness (LR+ 2.85) were moderately predictive, as were nocturnal symptoms (wheezing (LR+ 2.66), shortness of breath (LR+ 2.09), chest tightness (LR+ 2.34)), wheezing on auscultation (LR+ 2.35), and any reported wheezing (LR+ 2.60). A smoking history of < 20 pack years was only slightly predictive of asthma (LR+ 1.40). Although the onset of symptoms before the age of 20 years was the strongest predictor, it had a low sensitivity (42%) but high specificity (93%). A previous diagnosis of asthma and seasonal variation of symptoms had good sensitivities (84%-85%) and specificities (95%-83%).

Table 48: Univariable predictors of asthma in patients ≥ 15 years old with cough and difficulty breathing.

Variables	Sens, %	Spec,%	Crude likelihood ratios	
			LR+	LR-
Onset of symptoms before the age of 20 years	42	93	6.28	0.62
Previous diagnosis of asthma	84	85	5.79	0.18
Seasonal variation of symptoms	85	84	5.13	0.18
Past medical history of allergies	34	93	5.08	0.70
Day to day variability of symptoms	88	80	4.34	0.15
Symptoms triggered by emotions	44	89	4.05	0.62
History of hayfever	42	89	3.84	0.65
Onset of dyspnoea is episodic	54	86	3.75	0.54
Daytime wheezing	51	86	3.65	0.58
History of allergies	20	94	3.47	0.85
Symptoms triggered by environmental factors	64	80	3.16	0.45
Symptoms triggered by respiratory tract infections	54	83	3.16	0.55
Family history of asthma	62	78	2.86	0.48
Daytime tightness of chest	60	79	2.85	0.51
Nocturnal wheezing	57	78	2.66	0.54
Symptoms triggered by weather	75	71	2.61	0.35
History of wheezing	75	72	2.60	0.36
Symptomatic response to inhaled bronchodilator	89	64	2.50	0.17
Wheezing (audible or on auscultation)	55	77	2.35	0.59
Nocturnal tightness of chest	64	73	2.34	0.49
History of tightness of chest	77	65	2.20	0.35
Nocturnal shortness of breath	61	71	2.09	0.55
Symptoms worsened slowly over time	21	55	1.44	0.47
Not short of breath for most of the day	18	59	1.41	0.43
Smoking history of less than 20 pack years	83	41	1.40	0.41
Cough and sputum production did not precede onset of shortness of breath	15	62	1.37	0.40
Female	24	57	1.34	0.55
History of difficult breathing	94	26	1.28	0.23
No previous diagnosis of COPD	3	77	1.26	0.15
No past history of tuberculosis	9	83	1.11	0.49
No leg oedema in examination	3	91	1.07	0.31
Crackles heard on auscultation	4	87	0.32	1.10

8.3.4.1.2 Multivariable analysis of predictors of asthma: ≥15 years

Table 49 lists the significant multivariable predictors of asthma in patients 15 years and older as determined by logistic regression analysis after adjustment for non-dependence. A previous diagnosis of asthma (LR+ 2.27), onset of symptoms before the age of 20 years (LR+ 1.73), and an audible wheeze or wheeze on auscultation (LR+ 2.20) were most predictive. Reported symptomatic response to bronchodilator therapy, nocturnal dyspnoea, symptoms triggered by emotions, no worsening of symptoms over time, and no previous diagnosis of COPD were only moderately predictive (LR+ 1.47-1.32). If all 9 items (variables) were present in a patient ≥ 15 years with cough or difficult breathing then the (cumulative) likelihood of a diagnosis of asthma would be 81.8. In contrast, if all 9 variables were absent the patient would have a very slim likelihood of being asthmatic (LR- 0.01), and asthma can be virtually ruled out.

Table 49: Multivariable predictors for the diagnosis of asthma in patients ≥ 15 years (N=1354).†

	Likelihood ratio			
Diagnostic element	**Factor present**	**95% CI**	**Factor absent**	**95% CI**
Previous diagnosis of asthma.	2.27	1.69-3.01	0.53	0.42-0.67
Onset of symptoms before the age of 20 years.	1.73	1.39-2.08	0.81	0.90-0.90
Audible, or wheeze on auscultation.	2.20	1.72-2.76	0.61	0.52-0.72
Day to day variability of symptoms.	2.22	1.50-3.16	0.55	0.37-0.66
Nocturnal shortness of breath.	1.32	1.14-1.51	0.82	0.73-0.92
Symptoms triggered by emotions.	1.10	1.02-1.17	0.93	0.87-0.99
Response to bronchodilator	1.46	1.02-2.16	0.57	0.41-0.76
No worsening of symptoms over time.	1.46	1.02-2.16	0.55	0.52-0.75
No previous diagnosis of COPD.	1.47	1.16-1.84	0.42	0.20-0.83
Cumulative LRs (all 9 items)	81.8	17.7-42.3	0.01	0.01-0.21

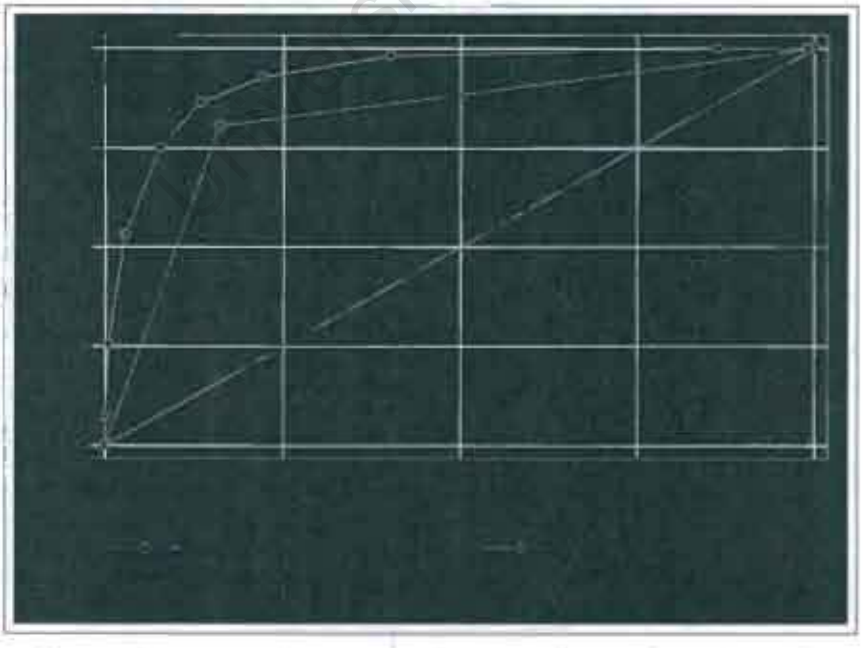
† 38 Patients had specialist diagnoses of asthma and COPD, therefore excluded from the multivariate analysis

The cut-off for a diagnosis of asthma in patients ≥ 15 years is ≥ 5 (Table 50). Therefore, if 4 or more symptoms are included in the derived model, then asthma can be diagnosed with a sensitivity of 86% and specificity of 87%. Figure 5 demonstrates the accuracy of the derived prediction rule (ARUC 0.93) compared to the accuracy of the nurse using the guideline (ARUC 0.81).

Table 50: Cut-point of derived multivariable model for predicting asthma.

Cut off point	Sensitivity, (%)	Specificity, (%)	Correctly Classified, (%)	LR+	LR-
≥0	100	0	35	1.00	
≥1	100	1	35	1.01	0.00
≥2	100	14	44	1.16	0.00
≥3	98	60	73	2.44	0.03
≥4	93	78	83	4.21	1.00
≥5	86	87	87	6.47	0.16
≥6	75	92	86	9.74	0.27
≥7	53	97	82	19.5	0.48
≥8	26	96	74	56.4	0.74
≥9	7	100	68	-	0.92

Figure 5: Performance of nurse using the guideline compared to the derived prediction rule for patients ≥15 years (ARUC) for a diagnosis of asthma.*



* chronasthn– nurse diagnosed asthma; aasthma – derived prediction model

8.3.4.2 Predictors of asthma: ≥ 15 years with asthma or COPD

8.3.4.2.1 Univariable analysis of predictors of asthma: patients with asthma or COPD.

Analysis of the univariable predictors for asthma in patients ≥ 15 years with obstructive lung disease revealed a number of variables strongly predictive of asthma Table 51. These were: onset of symptoms before the age of 20 years (LR+9.9), a previous diagnosis of asthma (LR+8.71), a history of hayfever (LR+6.95), seasonal variation of symptoms (LR+4.74), a history of allergies (LR+4.49), day to day variability of symptoms (LR+4.33).

Table 51: Univariable predictors of asthma in patients with obstructive airways disease (asthma or COPD).

Description	Sens, %	Spec, %	CRUDE	
			LR +	LR -
Onset of symptoms before the age of 20 years	42	96	9.90	0.61
Previous diagnosis of asthma	85	90	8.71	0.17
History of hayfever	42	94	6.95	0.62
Seasonal variation	85	82	4.74	0.19
History of allergies	20	95	4.49	0.83
Day to day variability of symptoms	88	80	4.33	0.15
No worsening of symptoms over time	21	21	3.70	0.27
Smoking history of less than 20 pack years	83	75	3.27	0.23
Family history of asthma	62	80	3.17	0.47
Not short of breath for most of the day	18	28	2.90	0.25
No cough and sputum production preceded	15	29	2.90	0.21
Female	24	35	2.19	0.37
No previous diagnosis of COPD	3	45	2.15	0.06
History of tightness of chest	77	52	1.60	0.44
Symptomatic response to inhaled bronchodilator	89	41	1.50	0.28
No history of cannabis use	11	67	1.33	0.33
Wheezing (audible or on auscultation)	55	55	1.22	0.82

* Sens: sensitivity; Spec: specificity

8.3.4.2.2 Multivariable analysis of predictors of asthma among patients with asthma or COPD

Multivariable logistic regression analysis showed that a previous diagnosis of asthma is a strong predictor (LR+ 4.03) of respiratory disease in patients ≥15 years with obstructive lung disease, followed by no report of gradual worsening of symptoms over time (LR+ 2.17) (Table 52). Other predictors of obstructive lung disease are a pack year history of < 20, day to day variability of symptoms, wheezing, and female sex (LR+ 1.42). The cumulative LR+ is 58, and the cumulative negative likelihood ratio is 0.01.

Table 52: Adjusted likelihood ratios for the diagnosis of asthma in patients with asthma or COPD. (N=800).†

	Adjusted likelihood ratio			
Diagnostic element	**Factor present**	**95% CI**	**Factor absent**	**95% CI**
Previous diagnosis of asthma.	4.03	3.03-5.18	0.21	0.16-0.28
No worsening of symptoms over time.	2.17	1.62-2.91	0.46	0.35-0.61
Pack year history of <20 years	1.80	1.31-2.48	0.48	0.36-0.7
Day to day variability of symptoms.	1.73	1.37-2.22	0.49	0.37-0.67
Audible, or wheeze on auscultation.	1.48	1.08-2.00	0.72	0.56-0.94
Female	1.42	1.05-1.85	0.70	0.53-0.95
Cumulative likelihood ratio (all 6 items)	58	32.2-105.1	0.01	0.01-0.20

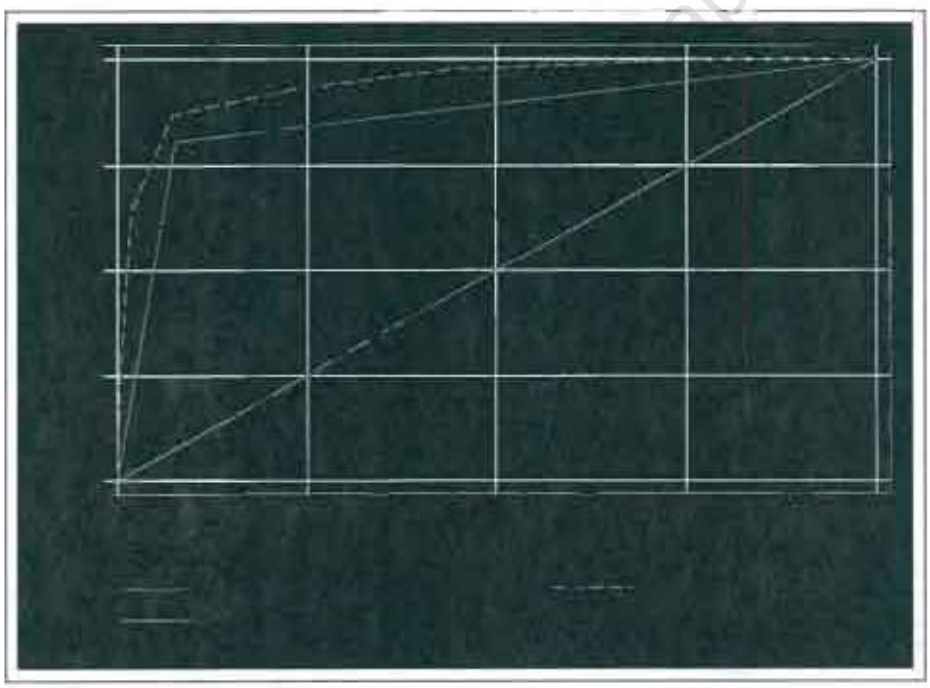
† 38 patients with specialist diagnoses of asthma and COPD, and 554 patients without asthma or COPD were excluded from the multivariate analysis.

The cut-off for the prediction rule is ≥4 (sensitivity 87%, specificity 93%, and the LR+ is 11.9) (Table 53). The ARUC under the curve is 0.95. Figure 6 shows that the derived rule is superior to the guideline algorithm as used by the nurse (ARUC 0.86).

Table 53: Cut-point of derived multivariable model for predicting asthma in patient with obstructive airways disease.

Cut off point	Sensitivity, (%)	Specificity, (%)	Correctly Classified, (%)	LR+	LR-
≥0	100	0	59	1.00	-
≥1	100	22	68	1.27	0.00
≥2	98	55	80	1.19	0.04
≥3	94	76	86	3.89	0.08
≥4	87	93	89	11.93	0.14
≥5	64	98	78	34.34	0.36
≥6	23	99	55	75.82	0.77

Figure 6: Performance of nurse using the guideline compared to the derived prediction rule for patients ≥15 years with obstructive airways disease (ARUC) for a diagnosis of asthma.



* chronasth – nurse diagnosis of asthma; asa–derived prediction model

8.3.4.3 Predictors of asthma: ≥40 years with asthma or COPD

8.3.4.3.1. Univariable analysis of predictors of asthma among patients ≥40 years with asthma or COPD

Univariable predictors of asthma in patients ≥ 40 years with asthma or COPD are presented in Table 54. Onset of symptoms before the age of 20 years (LR+8.67), a previous diagnosis of asthma (LR+6.83), seasonal variation (LR+4.60), day to day variability of symptoms (LR+4.17), no gradual worsening of symptoms over time (LR+3.82), and smoking less than 20 pack years (LR+3.42) were the strongest predictors. The absence of a bronchodilator response virtually ruled out asthma (LR-0.20).

Table 54: Univariable predictors of asthma in patients with obstructive airways disease (asthma or COPD) in patients over 40 years and older.

Description	Sens, %	Spec, %	CRUDE LR +	LR -
Onset of symptoms before the age of 20 years	44	95	8.67	0.6
Previous diagnosis of asthma	85	88	6.83	0.17
Seasonal variation	87	81	4.60	0.16
Day to day variability of symptoms	88	79	4.17	0.15
No worsening of symptoms over time	26	19	3.82	0.32
Smoking history of less than 20 pack years	84	76	3.42	0.22
Not short of breath for most of the day	22	28	2.83	0.30
Female	25	33	2.35	0.37
No cough and sputum production preceded	17	28	2.30	0.24
No previous diagnosis of COPD	4	44	2.18	0.07
Symptomatic response to inhaled bronchodilator	93	34	1.42	0.20

* Sens: sensitivity; Spec: specificity

8.3.4.3.2 Multivariable analysis of predictors of asthma among patients ≥40 years with asthma or COPD

The best predictors for the diagnosis of asthma among patients 40 years and older with obstructive lung disease are: a previous diagnosis of asthma (LR+ 4.14), no gradual worsening of symptoms over time (LR+ 2.26), a < 20 pack year history of cigarette smoking (LR+1.87), and day to day variability of symptoms (LR+1.82) (Table 55). If all 4 history variables were present in a patient ≥ 40 years with obstructive airways disease, then a diagnosis of asthma would be 40 times more likely. On the contrary if the items were absent the patient would unlikely to have asthma (LR- 0.01).

Table 55: Adjusted likelihood ratios for the diagnosis of asthma in patients over 40 years with asthma or COPD. (N=563).†

	Adjusted likelihood ratio			
Diagnostic element	**Factor present**	**95% CI**	**Factor absent**	**95% CI**
Previous diagnosis of asthma.	3.43	2.52-4.59	0.23	0.16-0.32
No worsening of symptoms over time	2.28	1.63-3.13	0.50	0.38-0.66
Pack year history of < 20 years	1.86	1.37-2.50	0.46	0.33-0.68
Day to day variability of symptoms.	1.83	1.39-2.40	0.44	0.31-0.64
Female	1.52	1.08-2.14	0.69	0.51-0.94
Cumulative likelihood ratio (all 5 items)	40	21.6-83.3	0.02	0.01-0.03

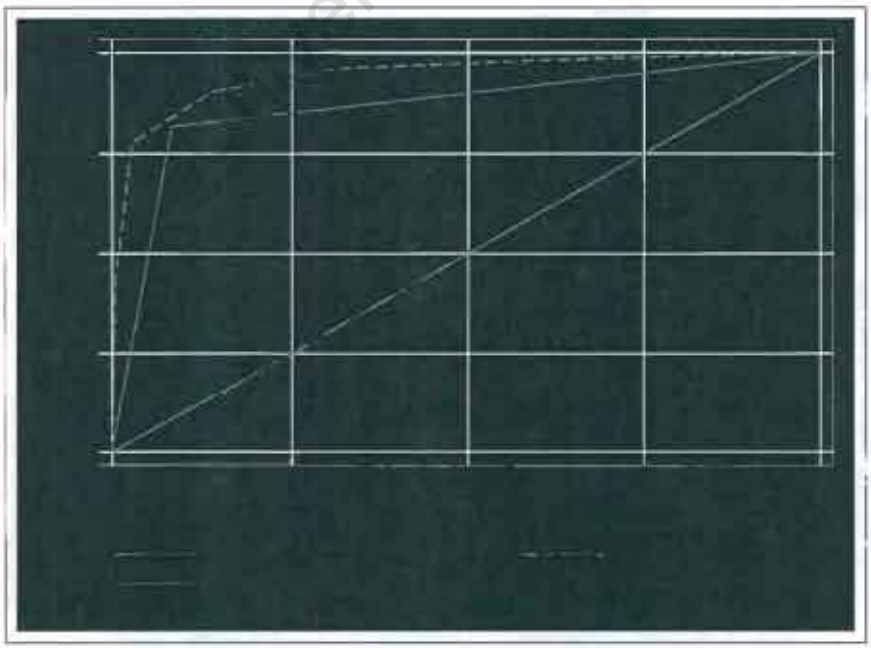
† 38 patients with specialist diagnoses of asthma and COPD, 554 patients without asthma or COPD, and 237 younger than 40 years were excluded from the multivariate analysis.

For the derived prediction model (Table 55), a cut-off of ≥ 3 out of the four items would yield a sensitivity of 90%, a specificity of 86%, and an ARUC of 0.95. The LR+ would be 6.54 (Table 56). A cut-off of ≥ 4 would increase the likelihood ratio, but decrease the sensitivity to 78%. Figure 7 illustrates the higher ARUC of the derived multivariable prediction model (ARUC 0.95) compared to the accuracy of the nurse using the guideline (ARUC 0.87).

Table 56: Cut-point of derived multivariable model for predicting asthma in patients ≥40 years with obstructive airways disease.

Cut off point	Sensitivity, (%)	Specificity, (%)	Correctly Classified, (%)	LR+	LR-
≥0	100	0	61	1.00	-
≥1	98	40	76	1.62	0.04
≥2	96	68	85	3.02	0.55
≥3	90	86	89	6.54	0.11
≥4	78	97	85	28.11	0.22
≥5	43	99	65	92.82	0.57

Figure 7: Performance of nurse using the guideline compared to the derived prediction rule for patients ≥40 years with obstructive airways disease (ARUC) for a diagnosis of asthma.



* chronasth – nurse diagnosis of asthma; aa-derived algorithm model

8.4 Chronic Obstructive Pulmonary Disease (COPD)

8.4.1 Accuracy of the nurse using guidelines in diagnosing COPD

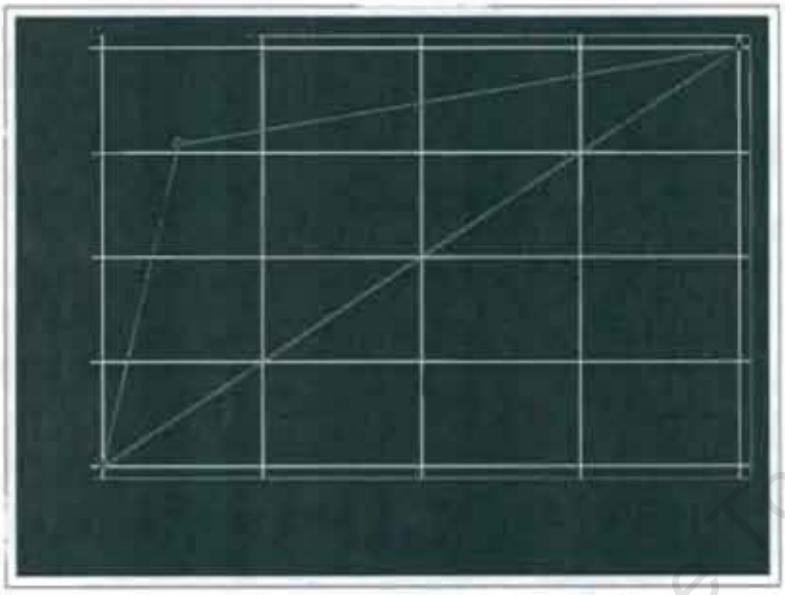
The overall accuracy of the guideline in diagnosing COPD (n=404), using the respiratory physicians' diagnoses as the reference standard (n=368) was satisfactory (Table 57). Its sensitivity was 77%, specificity was 88%, and area under the ROC curve was 0.84 (Figure 8).

Table 57: Diagnostic accuracy of nurse using the PALSA guideline in diagnosing COPD with the respiratory physicians' diagnoses as the reference standard.*

True positives, n	283
True negatives, n	903
False positives, n	121
False negatives, n	85
Sensitivity, % (95% CI)	77 (72-81)
Specificity, % (95% CI)	88 (86-90)
PPV, % (95% CI)	70 (65-74)
NPV, % (95% CI)	91 (89-93)
LR+	6.50
LR -	0.26
ARUC (95% CI)	0.84 (0.80-0.85)

PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-: negative likelihood ratio, ARUC: area under the receiver operating characteristics curve.
* Nurse diagnoses (n=404). Respiratory physician diagnoses (n=368)

Figure 8: Diagnostic accuracy of the nurse using the guideline to diagnose COPD with the respiratory specialists' diagnoses as the reference standard (ARUC).



8.4.1.1 False positive diagnosis of COPD

Asthma was the most common false positive diagnosis, representing 46% (33 of the primary and 23 of the additional diagnoses) of the 112 (30%; 100%-PPV) false-positive diagnoses of COPD made by the nurse (Table 58). Other common primary misdiagnoses were LRTI in 16 (13.2%), acute exacerbations in 19 (16.0%), chronic bronchitis in 13 (10.7%), and other lung conditions in 13 (10.7%) patients. Patients with additional diagnoses of asthma had LRTI (n=16-2, (12.5%)), cardiovascular disease (n=16-2, (12.5%)), and tuberculosis (n=7-1, (14.2%)) as their primary diagnoses.

Table 58: False positive diagnoses (COPD).*

Diagnostic categories	Primary specialist diagnoses, n (%)	Additional asthma diagnoses made as secondary, tertiary, or quaternary diagnoses by the specialist,* (n)
Asthma	33 (27.2)†	
Acute exacerbation	19 (16.0)	18
LRTI	16 (13.2)	2
Cardiovascular	16 (13.2)	2
Chronic bronchitis	13 (10.7)	
Other lung conditions	13 (10.7)	
TBS	7 (5.8)	1
Common cold	1 (0.8)	
Allergic rhinitis	1 (0.8)	
ENT	1 (0.8)	
Rheumatology	1 (0.8)	
Total	121 (100)	23

* The specialist physician could make a maximum of four diagnoses per patient.
† For the total number of asthma diagnoses add the asthma diagnoses made by the specialist as secondary, tertiary or quaternary diagnoses (n=23).

8.4.1.2 False negative diagnosis of COPD

False-negative diagnoses (9%; 100-NPV) made by the nurse instead of COPD included tuberculosis in 32 (38%), acute exacerbations in 18 (21%), asthma in 18 (21%); and as a secondary diagnosis, asthma in a further 21 (46% in total) signifying the degree of overlap between asthma and COPD (Table 59). Most additional asthma diagnoses were made for patients with tuberculosis (10 (31%)), acute exacerbations (10 (56%)), and only 1 (25%) for URTI.

Table 59: False negative diagnoses (COPD).*

Diagnostic categories	Primary nurse diagnoses, n (%)	Additional (secondary or tertiary) asthma diagnoses made by the nurse*, (n)
TBS	32 (38%)	10
Asthma	18 (21%)	
Acute exacerbation	18 (21%)	10
LRTI	8 (9%)	
Chronic bronchitis	4 (5%)	
URTI	4 (5%)	1
Non-PALSA**	1 (1%)	
Total	85	21

* The nurse could make a maximum of three diagnoses per patient.
** Diagnosis not classifiable by the PALSA guideline
† For the total number of asthma diagnoses, add the additional asthma diagnoses made by the nurse (n=21) to the total number of primary diagnoses

8.4.2 Accuracy of the guideline in determining levels of COPD severity

The guideline performed much better at diagnosing severe COPD than mild/moderate COPD (Table 60). However, for both mild/moderate COPD and severe disease, a positive nurse diagnosis rules in the condition, owing to the high specificity (specificities 93% and 87%, respectively).

Table 60: Distribution of diagnoses for each level of asthma disease control (N=1392).

Levels of severity	Mild/moderate COPD	Severe COPD
True positives	82	72
True negatives	1072	1117
False positives	84	164
False negatives	154	39
Sensitivity (95% CI)	35 (29-41)	65 (55-74)
Specificity (95% CI)	93 (91-94)	87 (85-89)
PPV (95% CI)	49 (42-57)	31 (25-37)
NPV (95% CI)	87 (85-89)	97 (95-96)
LR +	4.78	5.06
LR -	0.70	0.40
ARUC (95% CI)	0.64 (0.61-0.67)	0.76 (0.71-0.81)

PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-: negative likelihood ratio, ARUC: area under the receiver operating characteristics curve.

8.4.3 Prevalence of clinical examination features in patients with COPD

The prevalences of clinical examination features in patients with COPD are presented below (Table 61). Sixty four percent of patients were male; 22% reported asthma previously. Most reported difficult breathing and 32% had used mandrax (methaqualone-mixed with cannabis). Daytime dyspnoea, but not chest tightness or wheeze were frequently reported in most patients. Surprisingly, 61% reported a response to inhaled beta-agonists. 51% had never had an acute exacerbation with 34% reporting between 1 and 5 per year. Wheeze was heard in 47% of patients on examination.

Table 61: Prevalence of symptoms in patients with respiratory physician diagnosis of COPD (n=368).

Variables	Patients with specialist diagnosis, n (%)
Difficult breathing of any duration	343 (93)
Cough of any duration	323 (88)
Symptoms slowly worsened over time	289 (79)
Daily or frequent cough	276 (75)
Daytime shortness of breath	263 (71)
Short of breath for most of the day	262 (71)
Cough and sputum production preceded the onset shortness of breath	255 (69)
Daily or frequent sputum production	237 (64)
Male	236 (64)
Response to a bronchodilator	226 (61)
History of COPD	224 (61)
Daily cough	207 (56)
Difficult breath ≥ 2 weeks	261 (71)
Nocturnal cough	178 (48)
Cough ≥ 2 weeks	240 (65)
Wheeze on auscultation	172 (4)
Nocturnal shortness of breath	166 (4)
Nocturnal tightness of chest	161 (4)
Nocturnal wheeze	130 (35)
Daytime tightness of chest	125 (34)
Dagga use	119 (32)
Never used a bronchodilator before	118 (32)
Day to day variability	86 (23)
Daytime wheeze	85 (23)
History of asthma	80 (22)
Seasonal variability	78 (21)
Family history of asthma	75 (20)
Crepitations	47 (12)
History of hayfever	25 (7)
Known allergies	21 (6)
Number of exacerbations per year	
1-5 per year	122 (34)
≥5 per year	55 (15)
None	185 (51)
Smoking history	
Never	6 (2)
Former	138 (37)
Current	224 (61)
≥20 pack years	269 (73)

8.4.4 Analysis of history and examination predictors of COPD

8.4.4.1 Predictors of COPD: ≥ 15 years

8.4.4.1.1 Univariable analysis of predictors of COPD: ≥15 years

Table 62 lists the significant univariable predictors of COPD in patients ≥15 years. A previous diagnosis of COPD was the strongest predictor (LR+ 14.48), followed by cough and sputum preceding onset of dyspnoea (LR+ 4.11), ≥20 pack year smoking history (LR+ 4.07), and dyspnoea for most of the day (LR+ 3.44). Variables moderately predictive of COPD were symptoms worsening slowly over time (LR+ 3.33), history of cannabis use (LR+ 2.84), male sex (LR+ 2.38), and previously diagnosed tuberculosis (LR+ 2.31). Interestingly, daily frequent sputum production or cough (LR+ 1.83 and 1.48, respectively) were not strong predictors. The absence of features typically suggestive of asthma (allergies, family history, hayfever) were only minimally predictive of COPD (LR+ 1.10-1.36).

Table 62: Univariable predictors of COPD in patient's ≥15 years old with cough and difficulty breathing.

Variables	Sens, (%)	Spec, (%)	Crude likelihood ratios	
			LR+	LR-
Previous diagnosis of COPD	55	96	14.48	0.47
Cough and sputum production preceded	71	83	4.11	0.36
Smoking history of 20pack years or more	74	82	4.07	0.32
Short of breath for most of the day	72	79	3.44	0.36
Symptoms worsened slowly over time	79	76	3.33	0.28
History of cannabis use	33	88	2.84	0.76
Male	65	73	2.38	0.48
Previously diagnosed tuberculosis	25	89	2.31	0.84
Onset of symptoms after the age of 40 years	81	60	2.00	0.33
Daily or frequent sputum production	63	66	1.83	0.56
No previous diagnosis of asthma	10	52	1.75	0.20
No day to day variability of symptoms	20	49	1.64	0.40
No seasonal variation	18	53	1.56	0.38
Daily or frequent cough	74	50	1.48	0.52
No family history of asthma	20	59	1.36	0.48
No history of hayfever	6	73	1.28	0.23
History of difficult breathing	93	23	1.21	0.30
No history of allergies	5	87	1.10	0.35

* Sens: sensitivity; Spec: specificity

8.4.4.1.2 Multivariable analysis of predictors for COPD: ≥15 years

Table 63 lists the significant multivariable predictors of COPD in patients ≥15 years old. As for the univariable analysis (Table 62), a previous diagnosis of COPD was the strongest predictor (LR+ 3.46). A smoking pack year history of ≥20 years (LR+ 2.07), history of cannabis use (LR+ 1.29), previous diagnosis of tuberculosis (LR+ 1.32), and slow worsening of symptoms over time (LR+ 1.56) were included in the model. Cumulative positive likelihood ratio if all 9 symptoms were present is 62.3. A cumulative negative likelihood ratio of 0.02 virtually rules out COPD in patients without these features.

Table 63: Multivariable predictors of COPD in patients ≥15 years old with cough and difficulty breathing (N=1354).†

	Adjusted likelihood ratios			
Diagnostic element	**Factor present**	**95% CI**	**Factor absent**	**95% CI**
Previous diagnosis of COPD.	3.46	2.44-4.85	0.57	0.47-0.67
Pack year history of ≥20 years	2.07	1.64-2.55	0.55	0.45-0.67
History of cannabis use	1.29	0.96-1.68	0.83	0.67-1.03
Previously diagnosed and treated TB	1.32	1.18-1.46	0.45	0.31-0.64
Symptoms slowly worsened over time.	1.56	1.13-2.12	0.74	0.60-0.92
Cough and sputum production preceded onset of dyspnoea	1.31	1.10-1.55	0.61	0.43-0.84
Onset of symptoms after the age of 40 years.	1.87	1.27-2.73	0.84	0.76-0.93
Presenting complaint of difficult breathing	1.25	1.07-1.44	0.65	0.48-0.89
No previous diagnosis of asthma.	1.07	1.10-1.12	0.56	0.35-0.90
All 9 items	62.3	35.0-119.8	0.02	0.01-0.03

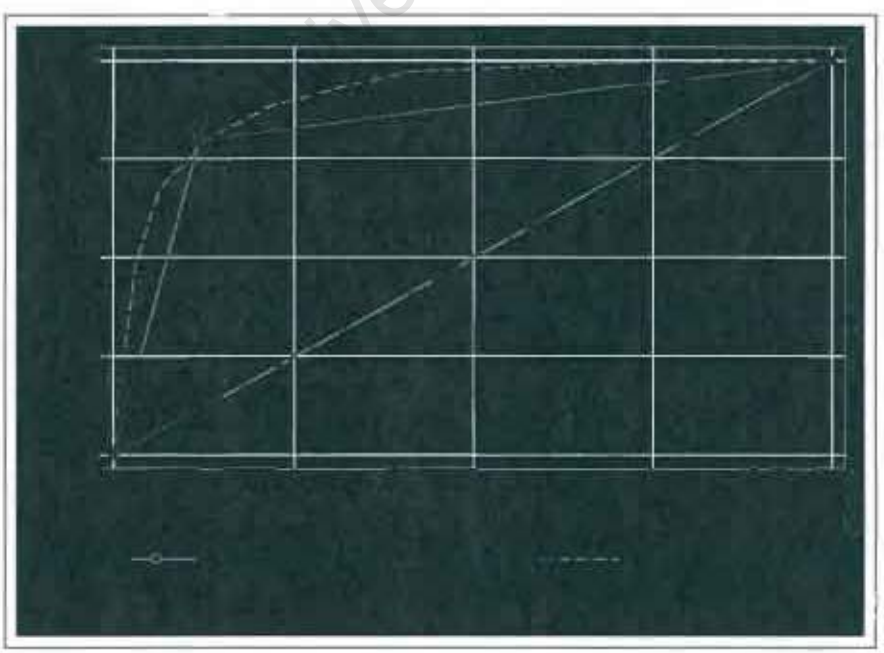
† 38 Patients had specialist diagnoses of asthma and COPD, therefore excluded from the multivariate analysis

The cut-off for a diagnosis of COPD in this category is ≥5 (Table 64). This value yields a sensitivity of 79% and specificity of 86%. Figure 9 compares the ARUC of the nurse using the guideline (0.84) to that of the derived prediction rule (ARUC 0.91).

Table 64: Cut-point of derived prediction multivariable model for predicting COPD.

Cut off point	Sensitivity (%)	Specificity (%)	Correctly Classified (%)	LR+	LR-
≥0	100	0.00	24	1.00	
≥1	100	1	25	1.01	0.00
≥2	99	30	47	1.42	0.01
≥3	97	59	68	2.38	0.04
≥4	88	78	81	4.03	0.15
≥5	79	88	86	6.35	0.23
≥6	68	94	87	10.48	0.34
≥7	49	97	85	15.61	0.52
≥8	16	99	79	18.61	0.84
≥9	4	99	77	40.33	0.96

Figure 9: Performance of nurse using the guideline compared to the derived prediction rule for patients ≥15 years (ARUC) for a diagnosis of COPD.



*chroncopd – nurse COPD diagnosis ; a-derived prediction model

8.4.4.2 Predictors of COPD: ≥ 15 years with asthma or COPD

8.4.4.2.1 Univariable analysis of predictors of COPD among patients with asthma or COPD

The best individual univariable predictors of COPD in patients with obstructive lung disease is a previous diagnosis of COPD (LR+ 16.2), cough and sputum production preceding dyspnoea (LR+ 4.67), dyspnoea for most of the day (LR+ 4.05), symptoms slowly worsening over time (LR+ 3.67), no symptomatic response to inhaled bronchodilator (LR+ 3.60), onset of symptoms after the age of 40 years (LR+ 3.57), and use of cannabis (LR+ 3.02) (Table 65). Previous tuberculosis (LR+ 2.92), male sex (LR+ 2.73), no reported wheezing (LR+ 2.29), and no history of tight chest (LR+ 2.26) were moderately predictive. The absence of individual features typically suggestive of asthma (hayfever, allergies, family history of asthma, atopy) virtually rules out COPD in this category.

Table 65: Univariable predictors of COPD in patients ≥15 years with obstructive lung disease (asthma or COPD).

Description	Sens, %	Spec, %	CRUDE	
			LR+	LR-
No day to day variability of symptoms	20	12	6.57	0.23
Previous diagnosis of COPD	55	97	6.20	0.46
No seasonal variation	18	15	5.36	0.21
No previous diagnosis of asthma	10	16	5.18	0.12
Cough and sputum production preceded	71	85	4.67	0.35
Smoking history of 20pack years or more	74	84	4.60	0.31
Short of breath for most of the day	72	82	4.05	0.35
Symptoms worsened slowly over time	79	79	3.67	0.27
No symptomatic response to inhaled bronchodilator	60	11	3.60	0.67
Onset of symptoms after the age of 40 years	81	77	3.57	0.25
History of cannabis use	33	89	3.02	0.76
Previously diagnosed tuberculosis	25	91	2.92	0.82
Male	65	76	2.73	0.46
No history of wheezing	42	25	2.29	0.57
No history of tightness of chest	48	23	2.26	0.63
No family history of asthma	20	38	2.13	0.32
Symptoms not triggered by environmental factors	30	36	2.00	0.47
No history of hayfever	6	58	1.62	0.14
No reported daytime wheezing	23	50	1.56	0.45
Symptoms not triggered by emotions	17	56	1.50	0.38
No history of allergies	5	80	1.20	0.22
No history of atopy	1	84	1.18	0.04

* Sens: sensitivity; Spec: specificity

8.4.4.2.1 Multivariable analysis of predictors of COPD among patients with asthma or COPD

No previous diagnosis of asthma (LR+ 4.09), a previous diagnosis of tuberculosis (LR+ 2.02), no reported variability of symptoms (LR+ 2.00), and slow worsening of symptoms over time (LR+ 1.84) were included in the reduced model (Table 66). If all 7 items were absent, the likelihood of having COPD would be very low (LR- 0.02). The cumulative LR+ was very high at 129.1.

Table 66: Multivariable predictors of COPD in patients ≥15 years with asthma or COPD. (N=800).†

	Adjusted likelihood ratios			
Diagnostic element	**Factor present**	**95% CI**	**Factor absent**	**95% CI**
No previous diagnosis of asthma	4.09	2.99-5.37	0.28	0.22-0.37
Symptoms slowly worsened over time.	1.84	1.38-2.44	0.40	0.40-0.73
No day to day variability of symptoms.	2.00	1.41-2.72	0.58	0.46-0.76
Pack year history of ≥ 20 years	1.97	1.41-2.73	0.59	0.46-0.77
Onset of symptoms after the age of 40 years.	1.54	1.20-1.96	0.57	0.41-0.79
Male	1.40	1.03-1.89	0.72	0.53-0.97
Previous diagnosis of tuberculosis	2.02	1.04-3.96	0.91	0.85-0.99
All 7 items present	129.1	52.3-319.0	0.02	0.01-0.03

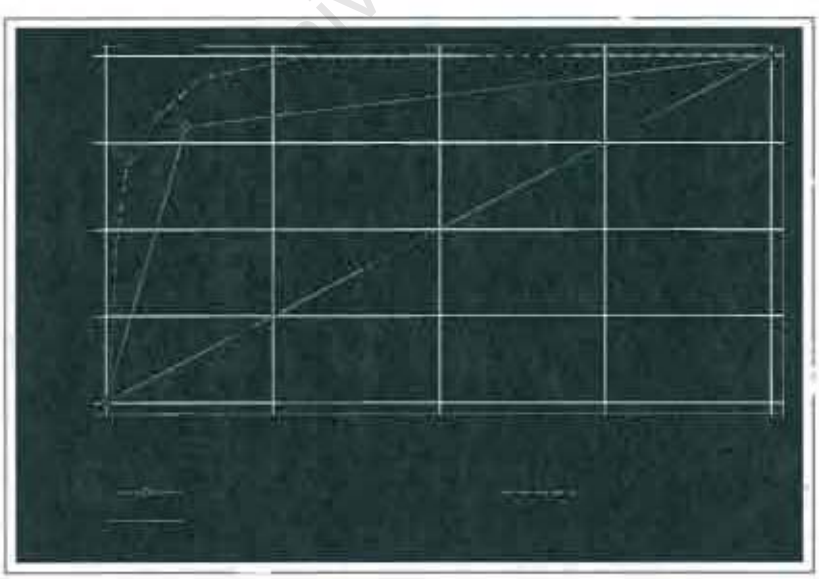
† 38 patients with specialist diagnoses of asthma and COPD, and 554 patients without asthma or COPD were excluded from the multivariate analysis.

The best cut-off for detecting patients with COPD among patients ≥ 15 years with cough or difficult breathing is ≥4 (sensitivity 82%, specificity 92%, LR+ 10.7) (Table 67). The prediction rule performs very well (ARUC 0.95) compared to the nurse using the guideline (ARUC 0.84) (Figure 10).

Table 67: Cut-point of derived prediction model for predicting COPD in patients with obstructive lung disease.

Cut off point	Sensitivity, (%)	Specificity, (%)	Correctly Classified, (%)	LR+	LR-
≥0	100	0	41	1.00	
≥1	100	35	62	1.53	0.00
≥2	99	74	83	3.47	0.01
≥3	93	86	89	6.64	0.07
≥4	82	92	88	10.72	0.19
≥5	67	97	85	22.48	0.34
≥6	44	98	76	29.70	0.56
≥7	8	99	62	13.29	0.92

Figure 10 Performance of nurse using the guideline compared to the derived prediction rule for patients ≥15 years with obstructive lung disease (ARUC) for a diagnosis of COPD



*chroncopd – nurse diagnosis; 6-derived prediction model

8.4.4.3 Predictors of COPD: ≥ 40 years with asthma or COPD

8.4.4.3.1 Univariable analysis of predictors of COPD among patients ≥40 years with asthma or COPD

The individual univariable symptoms most predictive of COPD in patients ≥40 years with obstructive lung disease were: a previous diagnosis of COPD (LR+ 14.8), no variability of symptoms (LR+ 6.82), no seasonal variation of symptoms (LR+ 6.24), no previous diagnosis of asthma (LR+ 5.83), no symptomatic response to bronchodilators (LR+ 5.13), a smoking pack year history of ≥20 (LR+ 4.64), and a history of cough and sputum production preceding onset of dyspnoea (LR+ 3.34) (Table 68). As in the analysis for the previous 2 categories, the absence of features typically suggestive of asthma rules out COPD. No previous diagnosis of asthma was a strong positive predictor (LR+ 5.83), and the presence of a previous diagnosis of asthma, strongly ruled out COPD in this category of patients (LR- 0.15).

Table 68: Univariable predictors of COPD in patients ≥40 years with obstructive lung disease (asthma or COPD).

Description	Sens, %	Spec, %	CRUDE	
			LR+	LR-
Previous diagnosis of COPD	56	96	14.84	0.46
No day to day variability of symptoms	21	12	6.82	0.24
No seasonal variation	19	13	6.24	0.22
No previous diagnosis of asthma	12	15	5.83	0.15
No symptomatic response to inhaled bronchodilator	66	7	5.13	0.71
Smoking history of 20 pack years or more	75	84	4.64	0.30
Cough and sputum production preceded	72	83	4.17	0.34
Onset of symptoms after the age of 40 years	79	79	3.74	0.27
Short of breath for most of the day	72	78	3.34	0.35
Symptoms worsened slowly over time	81	74	3.10	0.26
Male	68	75	2.68	0.43
Breathless on examination	53	77	2.27	0.62
No history of wheezing	36	28	2.27	0.51
No history of tightness of chest	41	28	2.15	0.57
No family history of asthma	17	39	2.14	0.28
Symptoms not triggered by environmental factors	34	34	1.95	0.51
No history of hayfever	7	59	1.57	0.17
No daytime tightness of chest	24	50	1.52	0.48
Symptoms not triggered by emotions	21	54	1.49	0.44
No daytime wheezing	14	9	1.46	0.35
No history of allergies	3	77	1.25	0.15

* Sens: sensitivity; Spec: specificity

8.4.4.3.2 Multivariable analysis of predictors of COPD among patients ≥40 years with asthma or COPD

The best predictors for this category are shown in Table 69. No previous diagnosis of asthma (LR+ 4.41), no day-to-day variability (LR+ 2.13), slow worsening of symptoms over time (LR+ 2.12), and a ≥20 pack year history of cigarette smoking (LR+ 2.07). The cumulative LR+ is 81.7.

Table 69: Multivariable predictors of COPD in patients ≥ 40 years with obstructive lung disease (asthma or COPD). (N=563).†

	Adjusted likelihood ratios			
Diagnostic element	**Factor present**	**95% CI**	**Factor absent**	**95% CI**
No previous diagnosis of asthma.	4.41	3.11-6.08	0.28	0.21-0.38
No day to day variability of symptoms.	2.13	1.46-2.99	0.57	0.43-0.75
Symptoms slowly worsened over time.	2.12	1.61-2.88	0.41	0.27-0.58
Pack year history of ≥20 years	2.07	1.40-2.92	0.56	0.42-0.76
Male	1.48	1.08-2.02	0.64	0.45-0.92
Reported wheezing	1.34	1.01-1.79	0.71	0.49-0.98
All 6 items present	81.7	38.3-173.3	0.02	0.01-0.04

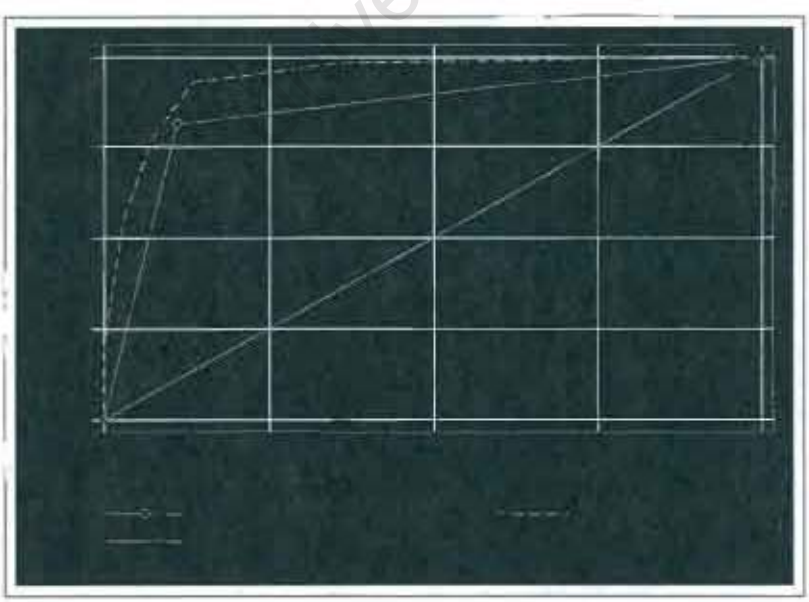
† 38 patients with specialist diagnoses of asthma and COPD, 554 patients without asthma or COPD, and 237 younger than 40 years were excluded from the multivariate analysis.

The cut-off for the derived multivariable prediction model above is ≥3 (Table 70). Therefore, if 3 out of the 6 items are present, the sensitivity is 93%, specificity 86%, the LR+ 6.85, and the ARUC is 0.94. The model performs better than the nurse using the guideline (ARUC 0.94) (Figure 11).

Table 70: Cut-point of derived prediction rule for predicting COPD in patients ≥ 40 years with obstructive airways disease.

Cut off point	Sensitivity (%)	Specificity (%)	Correctly Classified (%)	LR+	LR-
≥0	100	0	39	1.00	-
≥1	99	24	53	1.30	0.01
≥2	99	64	77	2.75	0.02
≥3	93	86	89	6.85	0.08
≥4	78	92	87	10.36	0.23
≥5	55	97	80	18.97	0.46
≥6	20	100	69	-	0.79

Figure 11 Performance of nurse using the guideline compared to the derived prediction rule for patients ≥40 years with obstructive lung disease (ARUC) for a diagnosis of COPD



*chroncopd – nurse diagnosis; c-derived prediction model

8.5 Acute exacerbations

8.5.1 Accuracy of the nurse using guideline in diagnosing acute exacerbations

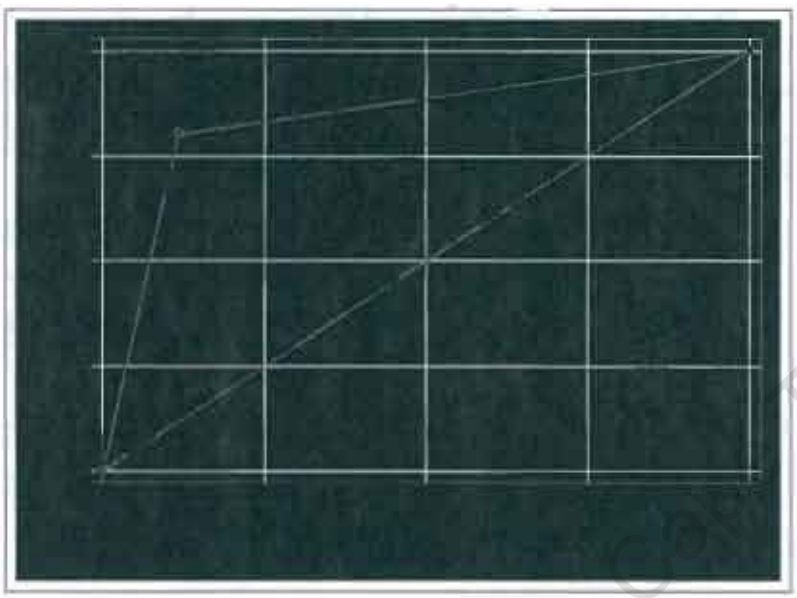
The nurse using the guideline (n=363) performed very well in diagnosing exacerbations of asthma or COPD using the respiratory physician as the reference standard (n=293) (Table 71). Its sensitivity was 80%, specificity was 88%, positive likelihood ratio was 6.89 and the area under the ROC curve was 0.84 (Figure 12).

Table 71: Diagnostic accuracy of the nurse using the PALSA guideline in diagnosing acute exacerbations using the respiratory physicians' diagnoses as the reference standard.*

True positives, n	235
True negatives, n	971
False positives, n	128
False negatives, n	58
Sensitivity, % (95% CI)	80 (75-85)
Specificity, % (95% CI)	88 (86-90)
PPV, % (95% CI)	65 (60-70)
NPV, % (95% CI)	94 (93-96)
LR+	6.89
LR-	0.22
ARUC (95% CI)	0.84 (0.82-0.87)

PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-: negative likelihood ratio, ARUC: area under the receiver operating characteristics curve.
*Nurse diagnoses (n=363). Respiratory physician diagnoses (n=293)

Figure 12: Diagnostic accuracy of the nurse using the guideline to diagnose acute exacerbations with the respiratory specialists' diagnoses as the reference standard (ARUC).



8.5.1.1 False positive diagnosis of acute exacerbations

Table 72 lists the distribution of the false negative diagnoses for COPD. Analysis of false positive acute exacerbation diagnoses by the nurse using the guideline demonstrated that these patients received a primary respiratory physician diagnosis (35%; 100%-PPV) of LRTI in 37% (47) of cases, of asthma in 23% (29), of COPD in 14% (18), of cardiovascular disease in 8% (10), and of other lung diseases in 10% (13). Patients with underlying asthma (46 (36%)) and COPD (27 (21%)), would have benefited from treatment for an acute exacerbation, and were at least recognised as having an obstructive lung disease. However, patients with LRTI, cardiac disease or other forms of lung disease, representing 56% of the false-positives would not.

In total more than half (57%) had obstructive lung disease. Of the asthma diagnoses, 23% (29) were primary diagnoses and 17 (17) were additional diagnoses (36% in total). For COPD, 14% (18) were primary and 7% (9) were additional diagnoses. In

addition, the nurse classified the following diagnoses as acute exacerbations: LRTI 37 (47), cardiac disease 8% (10), chronic bronchitis 2% (3), common cold 2% (3), allergic rhinitis 1% (1), suspected tuberculosis 2% (3), and infection 1% (1).

Table 72: Distribution of respiratory physician diagnoses* made when the nurse using the guideline incorrectly diagnosed acute exacerbation (false positive).

Diagnostic categories	Primary respiratory physician diagnoses, n (%)	Additional (secondary, tertiary, quaternary) asthma/COPD diagnoses made by the specialist*	
		Asthma†	COPD‡
Asthma	29 (23)†		
COPD	18 (14)‡		
Chronic bronchitis	3 (2)		
Common cold	3 (2)		1
LRTI	47 (37)	13	4
Allergic rhinitis	1 (1)		
TBS	3 (2)		2
Cardiac	10 (8)	4	1
Other lung	13 (10)		1
Infection	1 (1)		
Total	128 (100)	17	9

* The respiratory physician was permitted to make a maximum of four diagnoses per patient.
† For the total number of asthma diagnoses add the additional asthma diagnoses made by the respiratory physician (n=17) to the total number of primary diagnoses (n=29).
‡ For the total number of COPD diagnoses add the additional COPD diagnoses made by the respiratory physician (n=9) to the total number of primary diagnoses (n=18).

8.5.1.2 False negative diagnosis of acute exacerbations

Of the 58 (6%; 100%-NPV) patients with false-negative diagnoses, 86% (50) had obstructive lung disease: 50% (29) had asthma and 36% (21) had COPD (Table 73). Other diagnoses in this category were: common cold 5% (3), LRTI 10 (6), suspected tuberculosis 21% (12) and non-PALSA diagnoses 2% (1).

Table 73: Diagnoses made by the nurse in patients with respiratory physician diagnoses of acute exacerbation clinical syndrome (false negatives).

Diagnostic categories	Primary nurse diagnoses, n (%)	Additional (secondary or tertiary) asthma/COPD diagnoses made by the nurse*	
		Asthma†	COPD‡
Asthma	20 (34%)†		
COPD	16 (28) ‡		
Common cold	3 (5)	1	1
LRTI	6 (10)	2	
Non-PALSA	1 (2)		
TBS	12 (21)	6	4
Total	58 (100)	9	5

* The nurse could make a maximum of three diagnoses per patient. †

† For the total number of asthma diagnoses add the additional asthma diagnoses made by the nurse (n=9) to the total number of primary diagnoses (n=20).

‡ For the total number of COPD diagnoses add the additional COPD diagnoses made by the nurse (n=5) to the total number of primary diagnoses (n=16).

8.5.2 Frequency of symptoms for acute exacerbations

Table 74 lists the prevalences of the symptoms associated with mild/moderate and severe exacerbations. Of the variables used to determine the disease severity of the acute exacerbation, only accessory muscle use and respiratory rates ≥ 30 were more frequently associated with severe exacerbation. The frequencies of the remaining variables that determine disease severity were low for both diseases and therefore most likely did not contribute much to each diagnosis. Furthermore, the frequency of the symptoms and signs that suggest acute disease are similar between the two severity classifications.

Table 74: Frequency distribution of symptoms associated with mild/moderate and severe exacerbations.

Variables	Mild/moderate exacerbation (n=202), n (%)	Severe exacerbation (n=91), n (%)
Cough ≤ 2 weeks	162 (80%)	76 (84%)
Difficult breathing ≤ 2 weeks	160 (79%)	76 (84%)
Breathlessness while talking	7 (3%)	6 (7%)
Breathlessness while walking	96 (23%)	28 (31%)
Prominent accessory muscle use	18 (8%)	32 (35%)
Haemoptysis	6 (3%)	1 (1%)
Confusion	1 (0.5%)	1 (1%)
Agitation	1 (0.5%)	1 (1%)
Heart rate ≥120	3 (1%)	5 (5%)
Respiratory rate ≥ 30	7 (3%)	21 (23%)
Tight chest	164 (81%)	80 (88%)
History of wheeze	165 (82%)	79 (87%)
Wheeze on auscultation/audible	129 (64%)	79 (81%)

8.5.3 Analysis of history and examination predictors of acute exacerbations

8.5.3.1 Univariable analysis of predictors of acute exacerbations

The univariable predictors that best predict acute exacerbations are a history of atopy (LR+ 3.20), wheezing (audible or on auscultation) (LR+ 2.68), reported wheezing (LR+ 2.37), reported episodic dyspnoea (LR+ 2.29), and reported variation of symptoms (LR+ 2.16) (Table 75). A presentation of cough (LR+ 1.08), and no crackles heard on auscultation (LR+ 1.08) were only slightly predictive, but the negative LRs were 0.35 and 0.38, respectively.

Table 75 Univariable predictors of an acute exacerbation.

Description	Sens, %	Spec, %	CRUDE	
			LR +	LR -
History of atopy	14	96	3.20	0.9
Wheezing (audible or on auscultation)	69	74	2.68	0.41
History of wheezing	83	65	2.37	0.26
Episodic dyspnoea on presentation	66	71	2.29	0.47
Seasonal variation	70	68	2.16	0.44
Previous diagnosis of asthma	68	69	2.15	0.47
Use of bronchodilator more than twice a day	40	81	2.15	0.74
History of previous exacerbations	23	37	2.11	0.36
Symptoms triggered by respiratory tract infections	51	76	2.10	0.65
History of tightness of chest	83	60	2.05	0.28
Day to day variability of symptoms	73	64	2.02	0.42
Symptoms triggered by environmental factors	57	70	1.90	0.61
Symptoms triggered by weather	1	62	1.86	0.47
Symptoms triggered or worsened by exercise	56	69	1.82	0.63
History of difficult breathing	96	23	1.25	0.16
Symptoms triggered by emotions	37	81	1.20	0.78
Presenting complaint of cough	96	12	1.08	0.38
No crackles heard on auscultation	4	88	1.08	0.35

* Sens: sensitivity; Spec: specificity

8.5.3.2 Multivariable analysis of predictors of acute exacerbations

Only 4 items were included in the multivariable model (Table 76). Reported wheeze was the strongest predictor of an acute exacerbation (LR+ 2.15). The absence of these 4 items (LR- 0.08) virtually ruled out an acute exacerbation.

Table 76: Multivariable predictors of an acute exacerbation.

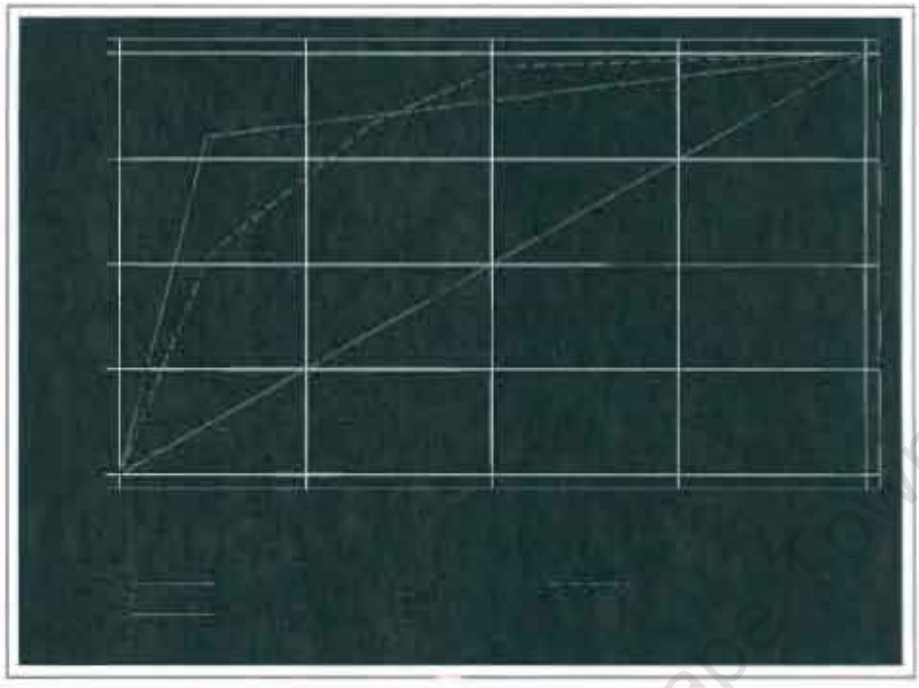
Diagnostic element	Adjusted likelihood ratios			
	Factor present		Factor absent	
History of wheezing	2.15	1.62-2.89	0.60	0.48-0.73
Wheezing (audible or on auscultation)	2.06	1.77-2.40	0.52	0.43-0.62
History of tightness of chest	1.35	1.13-1.56	0.59	0.42=0.81
No crackles heard on auscultation	1.07	1.02-1.11	0.44	0.20-0.79
All 4 items	6.38	5.06-7.80	0.08	0.03-0.15

The ARUC of the derived prediction rule is 0.82, with the best cut-off for the prediction of an acute exacerbation in a patient ≥15 years presenting with cough or difficult breathing being ≥ 3 of the 4 clinical features presented below. The sensitivity at this cut-off is 83%, and the specificity is 66% with a LR+ of 2.5 (Table 77). Figure 13 compares the accuracy of the nurse and derived prediction rules. There is very little difference between the two.

Table 77: Cut-point of derived prediction rule for predicting acute exacerbations.

Cut off point	Sensitivity, (%)	Specificity, (%)	Correctly Classified (%)	LR+	LR-
≥0	100	0	21	1.00	
≥1	99	7	26	1.07	0.04
≥2	97	49	59	1.89	0.63
≥3	83	66	70	2.46	0.25
≥4	52	88	80	4.35	0.54

Figure 13: Comparison of the accuracy of the nurse using the guideline and the derived prediction rule (ARUC) for acute exacerbations.



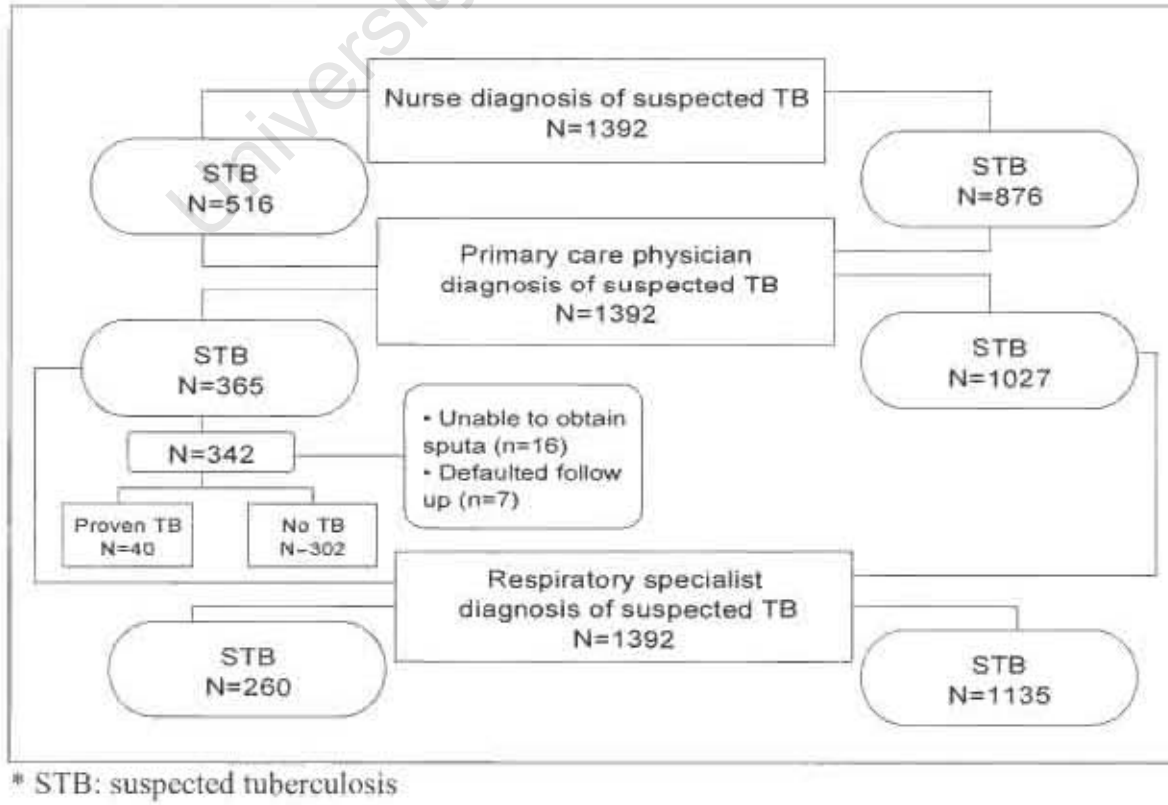
*acuteoldn-nurse diagnosis of acute exacerbation; a-derived prediction model

8.6 Tuberculosis

8.6.1 Distribution of suspected and bacteriologically-proven diagnoses of tuberculosis.

Figure 14 lists the distribution of tuberculosis diagnoses in the study. The primary care physician suspected 365 (26%) patients of having tuberculosis. Of these, sixteen (70%) were unable to produce sputa and 7 (30%) did not return their sputa samples. Of the remaining 342 for whom sputa were requested, 40 (12%) were proven to have tuberculosis: 24 (57%) had smear-positive tuberculosis, 5 (21%) had smear and culture-positive tuberculosis, 10 (24%) had culture-positive tuberculosis only, and 1 (2%) had smear-negative tuberculosis.

Figure 14: Distribution of tuberculosis diagnoses (suspected and bacteriologically-proven) in the study.*



* STB: suspected tuberculosis

8.6.2 Accuracy of guideline in diagnosing tuberculosis: primary care physicians as reference standard

The diagnostic accuracy of the nurse using the guideline as compared to the primary care physicians' diagnoses (Table 78) was as follows: sensitivity 76%, specificity 77%, PPV 53%, and a NPV of 90.

Table 78: Diagnostic accuracy of nurse using the PALSA guideline in diagnosing suspected tuberculosis to primary care physicians' diagnoses as the reference standard.

True positives, n	276
False positives, n	240
False negatives, n	89
True negatives, n	787
Sensitivity, % (95% CI)	76 (71-79)
Specificity, % (95% CI)	77 (74-79)
PPV, % (95%CI)	53 (49-58)
NPV, % (95% CI)	90 (88-92)
LR+	3.2
LR-	0.31
ARUC (95% CI)	0.76 (0.74-0.79)

PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-: negative likelihood ratio, ARUC: area under the receiver operating characteristics curve.
* Nurse diagnoses (n=516). Respiratory physician diagnoses (n=365)

8.6.3 Level of primary care physician confidence in the suspicion of tuberculosis

Of the 40 patients proven to have tuberculosis, the non-specialist assigned a level of certainty of 5 in 23 (58%) patients, whereas 1 (3%) and 3 (8%), respectively, were assigned values of 1 or 2 (Table 79). The certainty of diagnosis values for non-specialists was not significantly different from those of the specialists.

Table 79: Confidence of primary care physicians' in their diagnoses of suspected tuberculosis in proven and unconfirmed tuberculosis.

Levels of certainty	Tuberculosis suspected, not proven, n (%)	Tuberculosis suspected and confirmed, n (%)
1	28 (97)	1 (3)
2	73 (96)	3 (4)
3	79 (93)	6 (7)
4	58 (89)	7 (11)
5	64 (74)	23 (26)
Total patients	302 (88)	40 (12)

8.6.4 Accuracy of the nurse using guideline in diagnosing bacteriologically-proven tuberculosis

The sensitivity of the nurse using the guideline to detect patients with proven tuberculosis was 90%, specificity was 65%, PPV was 7%, and NPV was 99% (Table 80). Of the 4 patients not suspected of tuberculosis by the nurse, 1 had cough and difficult breathing, wheezing and tight chest for 1 day, another had these symptoms for 4 months, and yet another had cough and difficult breathing with pleuritic chest pain and new sputum production for 1 week. The fourth patient reported having only a cough and night sweats for 4 days. Two patients had previous diagnoses of asthma, and 1 of asthma and tuberculosis.

Table 80: Diagnostic accuracy of nurse practitioner using the PALSA guideline in diagnosing bacteriologically-proven tuberculosis (n=1392).

True positives, n	36
False positives, n	462
False negatives, n	4
True negatives, n	867
Sensitivity, % (95% CI)	90 (76-97)
Specificity, % (95% CI)	65 (63-68)
PPV, % (95% CI)	7 (5-10)
NPV, % (95% CI)	99 (98-100)
LR+	2.6
LR-	0.15
ARUC (95% CI)	0.78 (0.73-0.82)

PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-: negative likelihood ratio, ARUC: area under the receiver operating characteristics curve.
* Nurse diagnoses (n=516). Respiratory physician diagnoses (n=342)

8.6.5 Accuracy of guideline in diagnosing tuberculosis: using the respiratory physicians as reference standard

The respiratory physician assessed 262 (19%) patients as having suspected tuberculosis. The diagnostic accuracy of the nurse using the guideline compared to the respiratory physician diagnosis of suspected tuberculosis was as follows (Table 81): sensitivity 73%, specificity 71%, positive predictive value (PPV) 37%, negative predictive (NPV) 92%, and area under the ROC curve of 0.65. The primary care physician identified 152 more patients for tuberculosis screening than the respiratory physician, 6 of whom were later proven to have tuberculosis.

Table 81: Diagnostic accuracy of nurse practitioner diagnosis of suspected tuberculosis, compared to respiratory physician diagnoses of suspected tuberculosis (n=1392).

True positives, n	189
False positives, n	327
False negatives, n	71
True negatives, n	805
Sensitivity, % (95% CI)	73 (67-78)
Specificity, % (95% CI)	71 (68-74)
PPV, % (95% CI)	37 (32-41)
NPV, % (95% CI)	92 (90-94)
LR+	4.5
LR-	0.67
ARUC (95% CI)	0.65 (0.62-0.67)

PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-: negative likelihood ratio, ARUC: area under the receiver operating characteristics curve.
* Nurse diagnoses (n=516). Respiratory physician diagnoses (n=262)

8.6.6 Prevalence of symptoms and signs: suspected and diagnosed tuberculosis

Table 82 details the most common symptoms in patients proven to have tuberculosis. Cough (100%) followed by difficult breathing (70%), new sputum production (63%), loss of weight (50%), and night sweats (50%) were among the most common presenting symptoms.

Table 82: Prevalence of symptoms among patients confirmed to have tuberculosis (n = 40).

Symptom	Proven tuberculosis (n=40) , n (%)	Doctor suspected tuberculosis (n=365), n(%)	Specialist suspected tuberculosis (n=262), n(%)
Cough	40 (100)	97 (27)	97 (37)
Difficult breathing	28 (70)	77 (21)	73 (28)
New sputum production	25 (63)	54 (15)	43 (16)
Loss of weight	20 (50)	45 (12)	41 (11)
Night sweats	20 (50)	44 (12)	43 (12)
Pleuritic chest pain	11 (30)	16 (4)	19 (7)
Increased sputum production	6 (15)	13 (4)	13 (5)
Haemoptysis	5 (13)	13 (4)	14 (5)
Sputum colour change	5 (13)	8 (2)	7 (3)
Fever	2 (5)	3 (1)	5 (2)

8.6.7 Analysis of history and examination predictors of tuberculosis

Three independent features interrogated in the multivariate model predicted the diagnosis of tuberculosis. In decreasing order these were pleuritic chest pain, weight loss, night sweats (Table 83). The presence of all 3 items increased the likelihood 17-fold. The features associated with the diagnosis of suspected tuberculosis by the respiratory physician were haemoptysis, weight loss, night sweats, previous tuberculosis, pleuritic chest pain, absence of difficulty breathing, and absence of wheeze.

Table 83: Independent and combined likelihood ratios for predictors of suspected or diagnosed tuberculosis: logistic regression models.

Reference standard	Predictors	LR+	(95% CI)	LR-	(95% CI)
Tuberculosis suspected by respiratory physician*	Previous tuberculosis	2.6	(1.9-3.5)	0.75	(0.67-0.84)
	Haemoptysis	4.8	(2.2-10.3)	0.91	(0.86-0.96)
	Night sweating	2.8	(1.8-4.2)	0.77	(0.68-0.87)
	Weight loss	3.5	(2.3-5.6)	0.75	(0.66-0.84)
	Pleuritic pain	2.5	(1.5-4.1)	0.90	(0.84-0.95)
	No difficulty breathing	1.6	(1.2-2.1)	0.88	(0.80-0.96)
	No wheeze	1.2	(1.1-1.4)	0.70	(0.53-0.92)
	All 7 predictors	594	(232-1821)	0.22	(0.17-0.29)
Tuberculosis diagnosed by primary care physician**	Pleuritic pain	2.9	(0.2-4.79)	0.82	(0.63-0.99)
	Night sweats	2.9	(1.0-4.63)	0.81	(0.67-0.96)
	Weight loss	2.0	(1.0-4.6)	0.76	(0.54-0.97)
	All 3 predictors	17	(5.9-29.4)	0.50	(0.36-0.65)

* area under ROC curve for model=0.85. ** area under ROC curve for model=0.74

8.7 Lower Respiratory Tract Infection (LRTI)

8.7.1 Accuracy of the nurse using guideline in diagnosing LRTI

The guideline performed well at excluding LRTI (specificity 94%, NPV 85%), but had a low sensitivity of only 33% (Table 84). The positive likelihood ratio was 5.39 and the area under the ROC curve was 0.64 which is not high enough for a condition that requires specific therapy, namely antibiotics.

Table 84: Diagnostic accuracy of the nurse using the PALSA guideline in diagnosing LRTI, using the respiratory physicians' diagnoses as the reference standard.*

True positives, n	92
True negatives, n	1045
False positives, n	68
False negatives, n	187
Sensitivity, % (95% CI)	33 (27-39)
Specificity, % (95% CI)	94 (92-95)
PPV, % (95% CI)	56 (49-65)
NPV, % (95% CI)	85 (83-87)
LR+, % (95% CI)	5.39
LR-, % (95% CI)	0.71
ARUC (95% CI)	0.64 (0.61-0.66)

PPV: positive predictive value, NPV: negative predictive value, LR+: positive likelihood ratio, LR-: negative likelihood ratio, ARUC: area under the receiver operating characteristics curve.
* Nurse diagnoses (n=160); respiratory physician diagnoses (n=279)

8.7.1.1 False positive diagnoses of LRTI

The primary respiratory physician diagnoses when the nurse incorrectly diagnosed LRTI (44%; 100-PPV) were acute exacerbations in 30% (20 patients), COPD in 13% (9), other lung conditions in 13% (9), asthma in 10% (7), and cardiovascular disease in 10% (7) (Table 85).

Table 85: Distribution of primary respiratory physician diagnoses made when the nurse using the guideline incorrectly diagnosed LRTI (false positive diagnoses).

Diagnostic categories	Primary respiratory specialist diagnoses, n (%)
Acute exacerbations	20 (30)
COPD	9 (13)
Other lung conditions	9 (13)
Asthma	7 (10)
Cardiovascular disease	7 (10)
URTI	6 (9)
Suspected TB	6 (9)
Allergic rhinitis	2 (3)
Metabolic conditions	2 (3)
Total	68 (100)

8.7.1.2 False negative diagnoses of LRTI

Table 86 lists the distribution of the diagnoses made by the nurse instead of LRTI (15%; 100-PPV). Most patients were suspected of having tuberculosis (51%). Twenty three percent would have been treated for acute exacerbations, and only 10% were thought to have an URTI instead.

Table 86: Distribution of diagnoses when the nurse using the guideline missed a diagnosis of LRTI (false negative).

Diagnostic categories	Primary nurse diagnoses, n (%)
Suspected TB	95 (51)
Acute exacerbations	44 (23)
URTI	18 (10)
Asthma	13 (7)
COPD	12 (6)
Non-PALSA	5 (3)
Total	187 (100)

8.7.2 Analysis of history examination predictors of LRTI

8.7.2.1 Univariable analysis of predictors of LRTI

Table 87 shows that the univariable clinical features most predictive of LRTI in this population is a history of fever (LR+ 4.18). Although the presence of cough is only mildly predictive (LR+ 1.13), the absence thereof strongly rules out LRTI (LR- 0.09). The absence of reported difficult breathing (defined as dyspnoea, tight chest, or wheezing) (LR+ 3.59), reported pleuritic chest pain (LR+ 2.08), and sputum production (LR+ 2.06) were also significantly associated with LRTI. Of note, in the univariable analysis, the colour of the sputum was not a predictor.

Table 87: Univariable predictors of LRTI

Description	Sens, %	Spec, %	Crude LR +	LR -
History of fever	8	98	4.18	0.94
No difficult breathing on presentation	55	12	3.59	0.63
Pleuritic chest pain	13	94	2.08	0.93
Sputum production	60	71	2.06	0.57
No history of wheezing	23	49	1.57	0.45
No history of tight chest	31	46	1.50	0.56
No previous diagnosis of asthma	19	56	1.45	0.43
No wheezing (audible or on auscultation)	17	61	1.37	0.44
No previous diagnosis of COPD	6	81	1.16	0.34
Cough on presentation	99	12	1.13	0.09

* Sens: sensitivity; Spec: specificity

8.7.2.2 Multivariable analysis of predictors of LRTI

The multivariable predictors of LRTI included in the reduced model are presented in Table 88. History of fever (LR+ 4.20) and the absence of difficult breathing on presentation (LR+ 2.26) were still the strongest predictors of LRTI. Sputum production (LR+ 1.80) was mildly predictive. No reported asthma or COPD, and the absence of wheezing (LR+ 1.18) were only slightly predictive. But the absence of cough (LR- 0.17) virtually rules out the disease. The presence of all 7 items in an adult patient presenting with cough or difficult breathing increased the likelihood of LRTI 32-fold. Sputum history and a history of fever were included in the guideline algorithm.

Table 88 Multivariable predictors of LRTI.

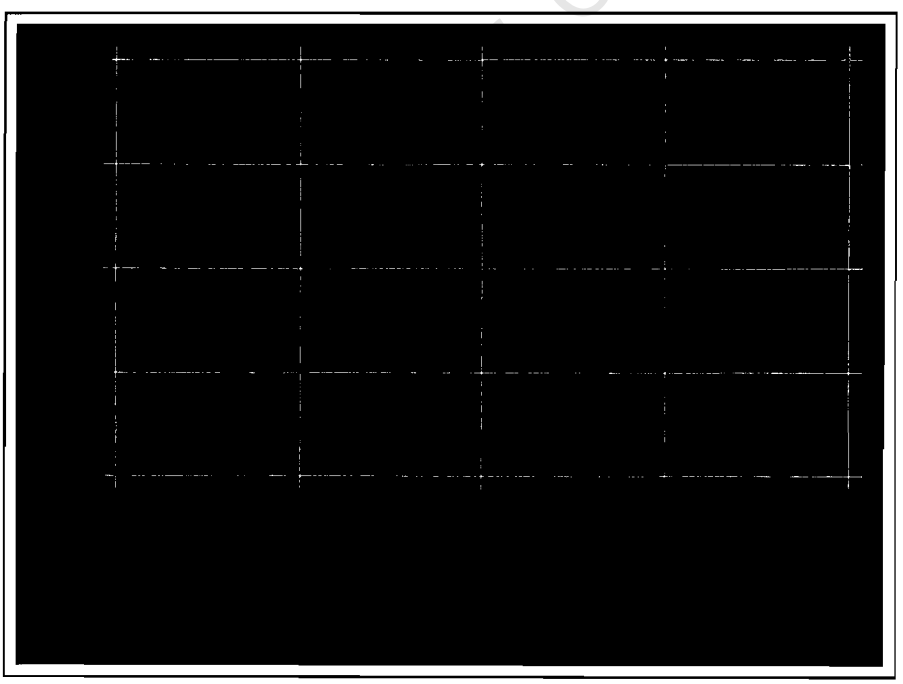
	Adjusted likelihood ratios			
Diagnostic element	**Factor present**	**95% CI**	**Factor absent**	**95% CI**
History of fever	4.20	1.84-8.78	0.94	0.90-0.98
No difficult breathing on presentation	2.26	1.78-2.86	0.74	0.66-0.82
Sputum production	1.80	1.53-2.13	0.63	0.53-0.73
No previous diagnosis of asthma	1.24	1.15-1.35	0.52	0.38-0.68
No previous diagnosis of COPD	1.20	1.11-1.30	0.41	0.24-0.63
No wheezing (audible or on auscultation)	1.18	1.07-1.30	0.64	0.48-0.84
Cough on presentation	1.06	1.03-1.09	0.17	0.05-0.42
All 7 items present	32	13.6-76.3	0.01	0.00-0.03

A cut-off of ≥5 has the most acceptable sensitivity and specificity (Table 89). Figure 15 shows that the derived prediction model performs better at detecting LRTI in this population than the nurse following the guideline algorithm (ARUC: 0.79 vs 0.69).

Table 89 Cut-point of derived multivariable model for predicting LRTI

Cut off point	Sensitivity, (%)	Specificity, (%)	Correctly Classified, (%)	LR+	LR-
≥1	100	0	20	1.00	
≥2	100	2	22	1.02	0.00
≥3	94	27	40	1.28	0.21
≥4	83	62	66	2.20	0.27
≥5	65	84	80	4.12	0.41
≥6	25	96	82	6.74	0.77
≥7	1	99	80	11.96	0.99

Figure 15 Diagnostic accuracy of the nurse using the guideline, compared to the derived prediction model (ARUC) for LRTI.*



* lrtin – nurse LRTI diagnosis; lrtia – derived prediction model

8.8 Upper Respiratory Tract Infection (URTI)

The performance of the guideline to detect URTIs is presented in Table 90. A total of 35 URTI's (TP (21) + FN (14)) were diagnosed by the respiratory specialist in this study. This is less than anticipated and limits the scope for analysis and conclusions regarding this category of disease. Therefore no formal analyses are presented.

Table 90 Diagnostic Accuracy of guideline to diagnose URTI.

True positives, n	21
True negatives, n	1280
False positives, n	77
False negatives, n	14
Sensitivity,% (95% CI)	60 (42-76)
Specificity,% (95% CI)	94 (93-95)
PPV,% (95% CI)	21 (14-31)
NPV,% (95% CI)	99 (98-99)
LR+	10.6
LR-	0.42
ARUC (95% CI)	0.77 (0.69-0.85)

8.9 Summary of results of the validation study

The guideline performed best at predicting acute asthma or COPD exacerbations, COPD, and asthma (sensitivities 77%-80%; specificities 84-88%, ARUC ≥0.81). It performed relatively well as a pre-screening test for tuberculosis (76% and 77%), using the primary care physician as the reference standard. For the diagnosis of bacteriologically-proven tuberculosis, the guideline in the hands of the nurse performed well (sensitivity 90%, specificity 65%), and only 4 patients were missed by the nurse. The guideline performed moderately well for diagnosing conditions which have milder symptoms, and/or those with a high degree of overlap of their symptoms (well-and moderately controlled asthma, mild/moderate COPD). Overall, the results for the individual disease syndromes fall within the following ranges: sensitivities, 33%-80%; specificities, 71%-94%; PPV, 21%-74%; NPV, 85%-99%; LR+, 4.83-10.6; LR-, 0.2-0.71; ARUC, 0.64-0.84).

False positive and false negative diagnoses for all diseases were at a minimum, with most diagnostic misclassification restricted to conditions that had clinical similarities, in particular for asthma and COPD. Detailed analysis of URTIs was not possible as the total number in the sample was too small.

The predictors for asthma in adults with cough or difficult breathing were: onset of symptoms before the age of 20 years, audible or auscultated wheeze, a previous diagnosis of asthma, day-to-day variability, symptomatic response to bronchodilators, nocturnal dyspnoea, symptoms triggered by emotions, no worsening of symptoms over time, no previous diagnosis of COPD (cut-off of any of ≥ 4 items yielded a sensitivity of 86% and specificity of 71%; LR+ 3). In adults with OAD the predictors of asthma were: a previous diagnosis of asthma, no worsening of symptoms over time, a pack year history of ≤ 20 years, day-to-day variability, audible or auscultated wheeze, and female sex (cut-off of any of ≥ 4 items yielded a sensitivity of 87% and specificity of 93%; LR+ 12). For patients ≥ 40 years with OAD the predictors of asthma were: a previous diagnosis of asthma, no worsening of symptoms over time, and a pack year history of ≤ 20 years, onset after the age of 40 years, female sex,

reported wheeze (cut-off of any of ≥ 3 items yields a sensitivity of 90% and specificity of 86%; LR+ 6.5).

The predictors for COPD in adults with cough or difficult breathing were: previous diagnosis of COPD; pack years smoking ≥ 20 years, cannabis use, previous diagnosis of tuberculosis, slow worsening of symptoms over time, cough and sputum production preceding onset of dyspnoea, onset of symptoms after the age of 40 years, dyspnoea on presentation, and no previous diagnosis of asthma (cut-off of any of ≥ 5 items yielded a sensitivity of 79% and specificity of 88%; LR+ 6). The predictors for patients ≥15 years with OAD were: no previous diagnosis of asthma, slow worsening of symptoms over time, no variability of symptoms, pack year history ≥ 20 years, onset after the age of 40 years, male sex, and a previous diagnosis of tuberculosis (cut-off of any of ≥ 4 items yielded a sensitivity of 82% and specificity of 92%; LR+ 11). And finally, for those ≥40 years with OAD were no previous diagnosis of asthma, no variability of symptoms, slow worsening of symptoms over time, a pack year history of ≥ 20 years, male sex, and reported wheezing (cut-off of any of ≥ 3 items yielded a sensitivity of 93% and specificity of 86%; LR+ 11).

For LRTI, predictors were: a history of fever, no difficult breathing, sputum production, no previous diagnosis of asthma/COPD, no wheezing, and cough on presentation (cut-off of any of ≥4 items yielded a sensitivity of 83% and specificity of 62%; LR+ 11).

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Chapter 9 : Discussion

9.1 Introduction

The approach adopted in the development of the PALSA guideline appears to have been successful judged both from the perspective of the target group, being the nurse practitioners and their managers. Its validity as a guide to syndromic diagnosis and management of respiratory diseases and tuberculosis has also been demonstrated. In developing and assessing the PALSA guideline, qualitative and quantitative research methods were combined. The qualitative research and review of relevant literature and documents informed its development, whereas the validation study served to validate the processes and outcomes of local adaptation by quantifying its accuracy.

The PALSA validation study is, to our knowledge, the first one of its kind to determine the accuracy of a locally-adapted guideline for diagnosing common respiratory conditions in adults presenting to primary care in a developing country. This study set out to test how close the guideline came to the alternative, a respiratory physician with access to special investigations. Its results confirmed the PALSA guideline's overall satisfactory performance as a diagnostic tool for detecting acute and chronic obstructive airways disease and LRTI; and as a pre-screening tool for patients with suspected tuberculosis. The PALSA guideline can therefore be viewed as an adequate solution for primary care with the potential for leading to earlier diagnosis and treatment of important respiratory conditions. Supporting nurses to provide early and more accurate treatment is a much better option in settings where patients would otherwise be required to wait until they could be transported to, or be seen in doctor-staffed clinics.

The analytical approach adopted in this study has been pragmatic, in that results were viewed not only from the perspective of 'correct' or concordant diagnoses, but also from the perspective of whether the potential benefits of early and correct diagnosis might outweigh the potential harmful consequences of an initial incorrect one.

Although complicated and speculative in parts, this detailed assessment of false positives and false negatives provides some reassurance that the nett result is positive. Ideally, this also needs to be tested in a pragmatic field study with examination of both process and health outcomes. It is also worth noting that although the respiratory physicians' diagnoses were considered the 'gold' standard, even they demonstrated an element of diagnostic uncertainty as evidenced by the moderate concordance between them for two conditions in this study (kappa values of 0.57).

The PALSA guideline's successes however are not unqualified, as several shortcomings are evident both in the approach used and in the tool itself. Some of these have been or will be addressed in future revisions of the guideline and training programme. Others will remain a weakness, and must be viewed as the 'cost' consequence of oversimplification of diagnostic processes, and of having to rely so heavily on nurses to perform functions which optimally should be performed by physicians. The latter deficiency is implicit in the use of integrated management programmes like PALSA and IMCI, as they owe their existence to the systematic problems in the distribution of health care in poorer countries and the need to address these. On the other hand, the exercise of researching the extent to which these problems can be overcome, and the need to offer the highest level of care to those who have no other health care alternatives, is both a humanitarian obligation and a challenging academic exercise.

Results of the randomized controlled study conducted in the Free State province, confirm the effectiveness of the PALSA guideline when implemented using the educational outreach strategy.[1] Approximately 1000 patients ≥15 years were included in both the intervention and control arms. Inhaled corticosteroid prescriptions were significantly higher in the intervention group (13.7% vs 7.7%; OR 1.90 (1.14-3.18) and were thought to be appropriate as more patients with inhaled corticosteroids reported a clinical response to bronchodilator therapy (85% vs 73%). A significant increase in tuberculosis case detection (6.4% vs 3.8%; OR 1.72 (1.04-2.85)), despite only a modest, non-significant increase in sputum testing in the intervention group (22.6% vs 19.3%; OR 1.22 (0.83-1.80)) was shown. Patterns of referrals to higher levels of care also improved significantly. Antibiotic prescribing rates however were not different between the two groups, but were said to be low overall. And no

differences in co-trimoxazole provision were shown. This finding was reported to reflect the erratic supply of this drug at the time.

Some aspects of the development and validation studies require further discussion, and these will be presented below.

9.2 DEVELOPMENT OF THE PALSA GUIDELINE

Local adaptation of existing international or national guidelines for local use, recently coined *trans-contextual adaptation* by the ADAPTE Working Group,[2 3] has been shown to improve the uptake and ownership of adapted guidelines.[4 5 6 7] This area of guideline development research is relatively new,[2] and the group calls for standardisation of guideline adaptation methods, and presents a potential framework.

At the time of the development of the PALSA guideline, no formal methods for guideline adaptation were published. Therefore, those proposed for de novo guideline development were employed and adapted for use by the PALSA guideline development group. When compared to the adaptation steps proposed by the ADAPTE group, many similarities are noted. These relate to those PALSA methods used to: form a multidisciplinary development group; define and assess the clinical question; search for and externally review other guidelines; tailor the guideline to local circumstances; and to ensure adequate adoption and endorsement of the PALSA guideline.

A major deviation of PALSA from methods used to either develop or adapt existing guidelines is that in the PALSA guideline, recommendations are evidence-based but are not graded to indicate how they are linked to their supporting evidence. This process is regarded by evidence-based guideline developers to be a very important step in the development of valid and explicit guidelines.[2 4 8] The decision to not employ this particular method could therefore be a potential weakness in the development of the PALSA guideline's recommendations. The reason underpinning this decision, however, was that qualitative research revealed a lack of understanding and knowledge of basic processes of care. Therefore it was assumed that inclusion of

a grading system might have not been effective in this setting. However, this is an assumption and must be tested in future studies. Knowledge support was however provided by the PALSA developers to the target users, as they were encouraged to submit 'frequently asked questions'. These were compiled and sent to the trainers on a monthly basis. The aim was to provide a scientific basis for those recommendations requiring clarification. This practice eventually lead to the compilation of a *Frequently Asked Questions* booklet. The inclusion of a grading system in the PALSA guidelines, and/or the provision of a detailed document showing exactly which evidence supports each recommendation are considerations for future revisions of the guideline.

Another deviation from methods proposed by evidence-based guideline development groups was that the PALSA guideline developers did not use formal decision-making processes to develop the final recommendations. These methods could have aided in improving the transparency of the developers' judgements[9] [10] and in how local policies and practices were applied.[11] [12]

9.2.1 The use of qualitative research for developing the guideline and its support materials

Integrating qualitative research into the development of the guideline, its support materials, and the chosen interventions provided detailed information about the acceptability and feasibility of its introduction into primary care in South Africa. These methods provided a depth of understanding of the local context and health practitioners' attitudes that mere review of the literature could, and often did, not provide. It also helped to identify barriers to the delivery of quality respiratory care locally. Futhermore, it served to determine how the PALSA guideline could be tailored to and integrated into current practices. In addition, areas needing improvement were highlighted (for example a change in the prescribing provisions for nurses) and served to inform changes in local policy. The deliberate emphasis on the use of qualitative research is considered to be a major strength in this study. The importance of the these methods in the development of multicomponent interventions, otherwise known as *complex interventions*, such as the one presented in this thesis

was emphasised in a document published by the Medical Research Council in the UK.[13] This document provides a framework for the development and evaluation of randomised controlled trials for complex interventions. It reports that qualitative research helps not only to inform the development of each component of the intervention, but also helps to more easily determine which component has contributed to the success or failure of the intervention as determined by the randomised controlled trial.

9.2.2 Limitations of the qualitative research methods

The focus group participants were chosen to be representative of those working in the setting in which the intervention was to be implemented. Inclusion of predominantly urban based health professionals could have therefore under-represented or excluded discussion of problems encountered by those working in rural areas. However, a prerequisite was that the participants have experience working in rural areas. Conducting more focus groups could also have provided more data, but the research team agreed that data saturation was reached as no new ideas emerged during the last focus group discussion. Patients were excluded from the qualitative evaluations and their inclusion could possible have provided more information. However, given the time and resource constraints, and the fact that the intervention was specifically targeted at nurses, a decision to not include them was made. Division of nurses and doctors into separate groups when conducting the focus group interviews was intended to increase the participation of members with shared work experiences and qualifications, and to reduce the effect of hierarchy on the groups' dynamics .[14]

9.2.3 Barriers to the delivery of respiratory disease care in South Africa

The main barriers to providing respiratory care were related to knowledge and skills, interprofessional relationships, and organisational issues. These findings are confirmed by the results of a number of other studies conducted in South Africa over the last two decades.[15 16 17 18 19] The existence of gaps and weaknesses in the training

and practices of nurses were also confirmed in a study evaluating the work practices of primary care nurses working in community clinics in South Africa.[20]

Other studies confirm the huge impact of organisational and interprofessional issues on nurses in primary care in South Africa, for example, a study in two local health districts showed that most nurses denied having had adequate managerial supervision.[21] One study conducted in the early-1990s reported that although most nurses actively participated in their daily activities, many reported very low levels of job satisfaction in comparison to most other professionals, but that despite this, their self-esteem was high. [22] Assessment of nurses' perceptions of the process of introduction of free health care revealed that the timing and degree to which they were involved in the introduction of health care policies directly influenced their involvement in helping to implement them.[23] In addition, most nurses felt excluded from the process of policy change and reported that resources were often insufficient to facilitate policy implementation. Finally, Thipanyana et al[24] reported that about half of the nurses working in primary care in two rural areas in South Africa reported heavy workload, and about three-quarters showed that clinic staffing ranged from average to poor. Together the results of these studies confirm the deficiencies so evident in South African primary care, and serve to further support the development of interventions to assist nurse practitioners.

Research on the barriers and facilitators to care in South Africa is lacking, and it is hoped that as the PALSA initiative expands, the group will conduct more studies in this area and will continue to design interventions to address them. Furthermore an effort will be made to, through consultation with policymakers, use past and future research to specifically address identified organisational and interprofessional barriers.

9.3 THE PALSA VALIDATION STUDY

9.3.1 Characterisation of the test population

The performance of any diagnostic test is dependent on the population mix and local disease prevalence in which it is validated.[25] The mix of respiratory diseases and co-morbid illnesses in the validation study is consistent with that found in a predominantly middle-aged adult population in South Africa.[26 27] The prevalence of past respiratory diseases, in particular, asthma (43%) and COPD (20%) was high, and 15% of patients had a history of previous tuberculosis. The latter, although high, is typically representative of the population that attends the study clinic, and reflects the high prevalence of tuberculosis in Cape Town which was estimated to be 638 per 100,000 in 2002.[28] The prevalence of cardiovascular disease was also particularly high (38%), with 10% of patients reporting a "metabolic disorder", usually diabetes mellitus. In most, this represents Type II diabetes, as obesity and the metabolic syndrome including insulin intolerance are common in this community. [29] Furthermore, the presence of multiple diagnoses on presentation seem to have further complicated the diagnostic process.

The first version of PALSA had little on HIV and AIDS. The reasons for this were three-fold. Firstly, when it was developed, anti-retrovirals were not available for patients in the public sector. Secondly, the provincial health authorities were in the process of developing guidelines for HIV diagnosis and management, and did not see these as part of a respiratory treatment package. Thirdly, it was considered overambitious to include HIV care in the first version, at least until the strengths and weaknesses of the approach had been tested. However, the almost immediate success of PALSA, in terms of its uptake and acceptability, prompted the expansion of the guideline to include HIV care (called PALSA Plus) even before the results of the randomised controlled trial were available.

PALSA Plus is currently being implemented and tested in two provinces in South Africa. In the version presented in this thesis, we included only the diagnosis of HIV infection and HIV-related respiratory complications. The prevalence of HIV infection in the suburbs served by the Retreat clinic in 2001 (estimated from anonymous testing of antenatal blood specimens) was 5.9%.[30] Although HIV testing was available at the clinic at which the study was conducted, it was not included in the design of the study.

9.3.2 Impact of the demographics and use of diagnostic categories in PALSA

South Africa's burden of tuberculosis is amongst the highest in the world, and the contribution of respiratory tract infections and obstructive lung diseases is high.[31] Although each condition was considered separately from the perspective of its diagnostic and management evidence-base, in the PALSA guideline they were also grouped according to whether or not they were acute or chronic. Furthermore they were grouped according to their degree of disease severity and shared symptoms and signs. This process resulted in the identification of 5 disease syndromes which were further divided into 26 potential 'diagnostic categories' for which separate distinct treatments were available.

9.3.3 Diagnostic accuracy of the PALSA guideline

The PALSA guideline's performance for diagnosing each disease compares favourably with that of other diagnostic questionnaires and algorithms, many of which consider only one or two conditions rather than the several in the PALSA guideline. It performed particularly well at detecting more severe conditions, or those with easily detectable clinical signs, for example wheezing in acute exacerbations and obstructive airways disease. Its performance for detecting respiratory tract infections was less satisfactory. Thus, in accordance with the IMCI validation studies,[32 33 34 35] results for conditions (such as pneumonia in children) which are easier to diagnose because of more obvious or specific clinical features seem to have higher sensitivities and specificities. Reported performances of other respiratory screening tools,[36 37 38 39 40 41 42] span a range of sensitivities from 23% to 86% and specificities between 40% and

100%. The derived predictors for obstructive lung disease and the results of the literature review, confirm that those history and clinical items included in the guideline were sufficient for making a diagnosis given the absence of spirometry. The performance of the guideline is best described disease by disease, and will be presented below.

9.3.3.1 Diagnostic accuracy of the guideline in diagnosing asthma

The PALSA guideline as used by the nurse performed well for the diagnosis of asthma (sensitivity 77%, specificity 84%). This compares favourably to the results of a study reported by Sistek et al,[43] in which the sensitivity and specificity of wheezing in combination with two out of three nocturnal symptoms (cough, dyspnoea, tight chest) were 80% and 86%, respectively. Sensitivities and specificities of symptom-based questionnaires to diagnose asthma in children ranged from 23% to 86% and from 55-100%, respectively.[39 40] This satisfactory performance can be attributed to the design of the guideline which included several ways of ensuring that asthma is considered and diagnosed. The guideline also provides an opportunity for distinguishing between asthma and COPD with a default to asthma if diagnostic uncertainty. A positive outcome of weighting the diagnosis towards asthma is that inhaled corticosteroids are introduced at an earlier stage, thereby reducing the possibility of exacerbations and even deaths from asthma.[44 45] A process of review within one month provides the opportunity for treatment to be stopped if ineffective or considered unnecessary. However, even in COPD, a trial of inhaled corticosteroids is considered an acceptable option as their use is associated with reduced exacerbations and hospitalisations in some patients.[46] According to the guideline the physician can, at the one month visit, decide whether to stop them or continue their use. Experience in resource-poor settings is that inhaled corticosteroid use is so low, that over-treatment is unlikely to reach wasteful proportions, as their cost is likely to be offset by savings of resources spent on treating exacerbations, including hospital admissions.[47 48]

The numbers of asthma or COPD cases that were either missed or misclassified by the nurse were small which suggests that the guideline was reasonably successful in

making the distinction between the two diseases. The guideline also appears to have two contrasting tendencies. The first was to diagnose (or default to) asthma instead of mild/moderate COPD; and the second was to diagnose severe COPD instead of asthma. The potential harm of incorrectly treating an asthmatic as COPD according to the guideline is that inhaled corticosteroids would be delayed for a period of one month until the patient is reviewed by a physician. Some of these patients may have had mixed disease (asthma and COPD) and may have benefited from asthma management.[49 50]

Several patients with LRTIs were diagnosed by the nurse as having asthma. Definitive diagnoses were not made for patients classified as LRTI, therefore the exact nature of the infection has not been reported. A possible explanation is that many of these patients had post-infectious cough due to postnasal drip or wheezing secondary to post-viral airways hyper-responsiveness. Post-infectious cough and wheezing typically continue for weeks after an upper respiratory tract infection and this time period falls outside the 2 week PALSA guideline cut-off for acute disease.[51] The observation that post-infectious cough is the most common cause of cough lasting between 3 and 8 weeks has led the American College of Chest Physicians to include a category of subacute cough in their clinical practice guidelines for the empiric management of cough.[52] They recommend that obstructive airways disease only be considered when post-infectious cough is excluded. Other diagnoses to be considered in the subacute category are pneumonia and acute exacerbation of chronic bronchitis. These findings have resulted in consideration of inclusion of post-infectious cough and post-viral wheezing in future revisions of the PALSA guideline.

More problematic is the tendency of the guideline to label patients with cardiovascular disease and other forms of lung disease not represented in the PALSA guideline as asthma. Cardiovascular disease was misdiagnosed as asthma by the nurse using the guideline in 15% of the cases. This finding is not surprising since nurses are neither trained nor expected to diagnose such conditions. Negative effects of this are possible delays in diagnosing heart disease, and treatment of these diseases with respiratory medications. The high prevalence in this community is grounds for altering the guideline to enable chronic heart disease to be distinguished from chronic lung diseases, and once again emphasizes the importance of local adaptation of the

guideline. Delay in diagnosing other lung conditions such as diffuse parenchymal lung disease, occupational lung disease (other than asthma) and carcinoma of the lung, while not ideal, is inevitable in this setting. These conditions frequently require radiology and physician input (often at specialist level) and, in some, biopsies and/or a trial of therapy. The overall prevalence of other forms of lung conditions not included in the guideline in this sample was low (2%), and the guideline made provision for referral of symptomatic patients not meeting the diagnostic requirements for the other conditions and those who did not improve on therapy. A small number of patients with asthma (11%) were diagnosed as suspected tuberculosis and would have undergone sputum testing, and then referral to a physician in the event of negative results. This small percentage of patients was unlikely to place a heavy burden on the tuberculosis programme, and the consultation with the physician might have resulted in their asthma being diagnosed.

9.3.3.2 Accuracy of the guideline in determining levels of asthma control

The guideline performed very well in diagnosing asthma as a syndrome, and at correctly identifying patients who did not fulfill criteria for each level of asthma control (specificities 87%-94%, NPV 89%-97%). However, it performed less satisfactorily at correctly classifying levels of asthma control as assessed by the specialist (sensitivities 27%-58%, PPV 17%-51%). As the level of control increased, the sensitivity of the guideline to make an accurate diagnosis increased, but at the expense of the specificity. These results highlight the difficulties in determining levels of disease control in the absence of more comprehensive questioning and lung function testing. Despite these poor results, further analysis of the levels of asthma control for each diagnostic category suggests that many patients may not have received the correct dosage of inhaled corticosteroids that matched the level of control, but would have received inhaled corticosteroids, albeit too high or too low a dose. Possible reasons for this are faulty training, and/or oversimplified categories of control. Assessment of the frequency of day time and nocturnal symptoms were the only criteria to determine control in the PALSA guideline.

Currently evidence-based recommendations for asthma management aim to assess asthma control, rather than levels of disease severity at each visit.[53 54 55 56] One reason for a change in classification is that asthma symptoms do not always correlate with the degree of asthma severity.[57 58] When the National Heart Lung and Blood Institute published their guidelines in 1991,[59] asthma severity was proposed to be assessed at the first visit with the assumption that the patient was treatment-naïve.[53] Asthma control however changes over time[60 61] and should therefore be assessed at every clinical encounter.[62 63] Assessing and managing the patient according to asthma control therefore has the added advantage of ensuring tailoring of treatment for each patient and makes the link between the current medication and level of control more explicit.[64 65] This allows for pharmacological treatment to stepped-up or down according to assessment of symptoms and other factors.

Six factors determine asthma control: asthma symptoms, sleep disturbance, use of rescue medication, limitations of daily activity, patient and physician overall assessment, and lung function.[52] Asthma can be well-or completely controlled. Well-controlled asthma is defined as having: (1) symptoms ≤2 times per week (2) use of bronchodilator for ≤ 2 times a week (3) no nocturnal or early morning symptoms (4) no limitation of daily activities (5) normal FEV1 or PEFR, and (6) patient and physician assessments of well-controlled asthma.[52] Complete or total control implies (2) symptoms, and/or (2) bronchodilator use for ≤ 2 times per week (3) no limitations of daily activities (4) no nocturnal or early morning symptoms (5) normal lung functions, and (6) physician and patient assessments of complete control. Treating asthma by determining the level of control will therefore be the new approach to asthma management and this is currently being promoted by GINA (personal communication Professor Eric Bateman). The revised PALSA Plus guideline has included a more comprehensive assessment of the level of asthma control, as adapted from a more recent publication.[53] Further research into the added value and feasibility of peak flow meter measurements in primary care in South Africa is needed to clarify its utility for nurses.

9.3.3.2 Clinical predictors of asthma

Categorical distinctions were made when assessing predictors for asthma for ease of comparison to studies reported in the medical literature, and to determine whether the diagnostic criteria for asthma and COPD should be refined. On univariable analysis, onset of symptoms before the age of 20 years and self-reported asthma were the strongest predictors for all three categories. Some authors argue that inclusion of self-reported diagnoses of asthma or COPD in a prediction model limits its generalisability to other populations, and is reliant on patient recall.[43] Others argue that it is a component of the clinical examination and should be included.[66] In agreement with the latter argument, it was included in this analysis. The only items present in each multivariable model were a previous diagnosis of asthma, and no worsening of symptoms over time. Reported wheezing of any kind did not perform as well as audible wheezing at predicting asthma. The strong predictive ability of the latter variable in this study could be a reflection of the inclusion of patients with acute exacerbations. 'History of wheeze' which referred to ever having had a history of wheezing, on the other hand, was most likely excluded from the model due to correlation with other variables (covariates). Reported wheezing with or without nocturnal symptoms or breathlessness has previously been reported to strongly predict asthma in a number of studies.[43 67 68 69] Exclusion of audible wheezing from the ≥40 years obstructive lung disease model could have been due to the increased prevalence of wheezing in patients in this category, suggesting that wheeze is not useful at distinguishing between asthma and COPD in older patients with obstructive lung disease. Wheezing was shown to be a predictor of asthma,[43 68 69] of COPD,[70] and of obstructive airways disease[71] in other studies. Reduced breath sounds have also been shown to be a strong predictor of asthma[72] but this variable was not included in this analysis because most nurses in primary care do not have auscultation skills. However, the excellent performance of 'audible or auscultated wheeze', prompts consideration of its inclusion in the next version of the PALSA guideline.

Other studies reporting on predictors to distinguish between asthma and COPD among patients ≥40 years, confirm that decreasing age, absence of smoking history, low cumulative pack years, and no report of worsening of dyspnoea over time are more suggestive of asthma.[36 42] Only one also reported wheezing (in the absence of an URTI) to distinguish between the two conditions in patients ≥45 years.[36] Cough and/or difficult breathing, defined as breathlessness on rest or activity, wheezing,

and/or tight chest, were entry points into the guideline. Although studies have shown that asthma is one of the commonest causes of chronic cough (which may or may not be associated with dyspnoea and wheezing),[73] and that up to 36% of patients may have these symptoms simultaneously,[74] cough was not a strong predictor.[75] The latter was probably due to these symptoms being common features of other respiratory and cardiovascular conditions.

Most of the studies discussed above however were not population based, were retrospective, and did not prospectively validate their findings. In this study all relevant history and clinical items were incorporated into the structured record form not just those presented in the guideline. This was intentionally done as to determine whether items not included in the guideline would prove to be predictive of asthma. In support of the PALSA guideline, results suggests that the guideline items are sufficient for diagnosing asthma in the absence of spirometry, as no new items other than that found in the guideline were included in the multivariable models.

9.3.4 Diagnostic accuracy of the guideline in diagnosing COPD.

The diagnosis of COPD is usually confirmed by spirometry.[46] An accurate diagnosis is however important from a public health perspective as the incidence of COPD secondary to tobacco use is rising steadily in South Africa and in developing countries throughout the world.[76] Despite the absence of spirometry, the guideline performed very well (sensitivity 70% and specificity 88%). This compares favourably to the results of two studies to determine predictors of COPD among patients ≥40 years,[42 72] which yielded sensitivities between 67% and 80% and specificities between 72% and 98%.

Features in the guideline prompting the nurse to diagnose COPD are cough and/or shortness of breath, wheezing or tight chest which started in later life (usually after the age of 45 years), and slowly worsening of dyspnoea over time. Other suggestive features are a longstanding history of cough and sputum production usually before the onset of the shortness of breath, dyspnoea for most of the day rather than in episodes,

and a smoking history of 15 years or more. As is the case in asthma, an opportunity to diagnose COPD in those with acute presentations is also presented.

In general the number of COPD diagnoses which were missed or misclassified were small. The most frequent false positive diagnosis was asthma. Given the small numbers of patients falsely diagnosed, and that newly-diagnosed patients are eventually to be seen by a physician for diagnostic confirmation, the costs of this misclassification can be speculated to be minimal. The misdiagnosis of COPD as tuberculosis is partly understandable, particularly in patients with a chronic bronchitic element, or in those who had systemic features of COPD such as wasting and loss of appetite. If the tuberculosis diagnostic algorithm is adhered to, patients shown to not have tuberculosis on sputum bacteriology testing will inevitably be referred to a physician for definitive diagnosis. Only 9% of COPD patients were thought to have LRTI which could have lead to inappropriate antibiotic prescriptions in this group, and could have delayed the diagnosis of COPD in these patients.

9.3.4.1 Clinical predictors of COPD

The predictors of COPD regardless of age and underlying obstructive lung disease were as follows: no previous diagnosis of asthma, slow worsening of symptoms over time, a ≥20 year pack history of COPD, and onset of symptoms after the age of 40 years. These results are consistent with those of other studies.[42] [36] [77] [78] Other predictors (for COPD among patients with obstructive disease regardless of age) were male sex and absence of day-to-day variability. Auscultated wheeze was an independent predictor of COPD among patients ≥40 years with obstructive lung disease.

In contrast to other studies, a previous diagnosis of tuberculosis and use of cannabis were strong predictors of COPD in this population. In Cape Town, cannabis is reported to be the most commonly used illegal drug,[79] with the prevalence among high school children estimated to be 7%.[80] In a recent population survey in a low-socioeconomic urban community in Cape Town, 11.3% people reported having used cannabis.[81] Many cannabis smokers also combine this drug with methaqualone, known as 'white pipe'.[80] The relationship between cannabis and lung injury and airflow limitation has been well described,[82] [83] [84] [85] although epidemiologic evidence of its link to COPD is speculative.[82] Cannabis use is also associated with an increased prevalence of cough, sputum production, wheeze, exercise-induced dyspnoea, and nocturnal symptoms.[82] [84]

Tuberculosis was another independent predictor of COPD. The association between tuberculosis and airways obstruction have been shown in a number of studies conducted in South Africa.[86] [87] In a paper by Ehrlich et al, the authors report that recognition of tuberculosis as a risk factor for airflow obstruction has not been widely acknowledged and call for more research to determine the exact pathophysiology underlying this condition.[88] In another study conducted by Ehrlich et al, a history of tuberculosis was the strongest predictor for chronic bronchitis, which confirmed findings of another South African study showing increased frequency of cough and/or sputum in previously treated tuberculosis patients.[89] Further research is needed in this

area as tuberculosis prevalence is high in South Africa. Failure to recognise the role that it plays in the development of chronic airways disease will only serve to further increase the local burden of respiratory disease.

9.3.5 Accuracy of the guideline in diagnosing acute exacerbations of asthma or COPD

Overall, the guideline performed best at detecting exacerbations of obstructive lung disease (sensitivity of 80% and a specificity of 88%). This might be explained by a number of factors, namely that the clinical features constituting this diagnosis are usually reported as being of sudden and of recent onset, and that most patients usually report a history of chronic obstructive airways disease on presentation. Because of the similarities in the acute presentations and initial treatments of asthma and COPD, PALSA makes no distinction between them.

Not surprisingly, LRTIs were frequently misdiagnosed as acute exacerbations. This means that these patients would have received inhaled beta-agonist as initial therapy, and not antibiotics. This perhaps is the most serious consequence of imprecise diagnoses, but is probably unavoidable within the constraints of clinics without physicians to check diagnoses, or those without radiology services. It is to be hoped that some of these patients will return if initial treatment fails to result in improvement. In addition, the diagnosis of LRTI includes bronchitis with purulent sputum.

A number of patients with chronic presentations of asthma and COPD were assessed by the nurse as having acute exacerbations. In the guideline an opportunity is provided to assess for underlying asthma or COPD. We therefore assume that the patient would have received the appropriate therapy as part of their long term asthma control. One reason for the difficulty in distinguishing between the acute and chronic disease presentations could have been the rigid definition that designates an exacerbation of longer than 2 weeks duration a chronic rather than an acute event. Important conditions that the guideline incorrectly diagnosed as acute obstructive lung diseases exacerbations were cardiovascular disease and other acute and chronic lung

diseases not included in the guideline. These patients might in some instances have received inappropriate and possibly harmful prescriptions of oral corticosteroids.

The most common diagnoses made by the nurse instead of acute obstructive airways disease exacerbations were chronic presentations of asthma or COPD. Treatment would however have included inhaled beta-agonist therapy for all, inhaled corticosteroid therapy for asthma, and a short-course of oral corticosteroids for patients assessed as having uncontrolled asthma or infective exacerbations of COPD. In most cases this would have been helpful if not ideal.

9.3.5.1 Clinical predictors of an acute exacerbation

Not surprisingly, reported wheeze, audible wheeze or wheezing on auscultation, reported tight chest, and the absence of crepitations on auscultation were indicators of an acute presentation. Exclusion of crepitations from the model did not change its accuracy, therefore the presence of the first 3 variables have a reasonably good accuracy at detecting acute exacerbations, particularly in our setting where nurses are not skilled at auscultation. Inclusion of reported wheeze and tight chest in the model yielded an accuracy of 0.76.

9.3.6 Accuracy of the guideline in suspecting and diagnosing tuberculosis

Identification of patients with possible pulmonary tuberculosis who require sputum examination is one of the major objectives of the PAL and PALSA programmes. One of the aims when developing the guideline was therefore to increase primary care nurses' suspicion of tuberculosis amongst patients presenting with signs and symptoms of respiratory diseases and to prompt bacteriological screening. Identification of such patients was thus not strictly a "diagnosis" but rather a 'pre-screening' test for employing a diagnostic method, namely sputum examination. Even the specialist diagnosis may be regarded as a screening 'method' rather than a definitive diagnosis, as bacteriologic confirmation is necessary. The diagnostic accuracy of the guideline in the hands of the nurse was assessed against the non-

specialist's diagnosis, and then against bacteriologically-confirmed tuberculosis. Because sputum testing was only performed on patients suspected of having tuberculosis by the primary care physician, these results are more useful for showing that the nurse identified all or most of the patients whom a doctor with access to radiology and a more detailed history identified as tuberculosis suspects.

The fact that the nurse using the guideline demonstrated a high degree of accuracy when compared to the specialist and primary care physicians, validates the syndromic 'diagnosis' for identifying patients requiring screening for tuberculosis. High sensitivity is achieved at the expense of specificity. Thus, while it is unlikely that a 'positive' case is missed, the low specificity results in additional effort and expenditure on false positive patients. In the case of tuberculosis, this results in additional use of resources for sputum examination. This is reflected in the ratio of suspected to bacteriologically-confirmed cases which for the nurse using the guideline was 13:1, compared with 9:1 and 5:1 for the primary care and respiratory physicians, respectively. These values compare satisfactorily with the ratio for high prevalence populations of 10:1 recommended for high prevalence countries.[90]

While the performance of the PALSA guideline was satisfactory in the population in which it was tested, it is recognised that the efficiency of a screening test is influenced by disease prevalence, which in this study was 3%. If the tuberculosis prevalence had been higher, the yield from screening would have been higher. Conversely, in lower tuberculosis prevalence settings the yield from screening would be lower. The current guideline therefore appears appropriate for primary care conditions in South Africa.[91]

9.3.6.1 Use of the two-week cut-off

According to WHO, a tuberculosis suspect is defined as an individual with a cough for 3 weeks or more.[92] The 3 week cut-off for classification of a tuberculosis suspect has been shown by many studies to be a robust indicator for screening for tuberculosis[93 94 95] Recently a study conducted in India compared the detection of smear-positive cases among out-patients with cough ≥2 weeks or ≥ 3 weeks.[96] Using ≥ 2 weeks yielded a case detection rate of 481 per 100 00 new adult out-patients

compared to 328 per 100 00 patients for ≥ 3 weeks cough. Using this criterion also resulted in an increase in the number of patients with chest symptoms (1371-2210) and an increase of 46% in the detection of smear-positive cases. More than a third reported cough for ≥ 2 weeks, but less than 3 weeks. A third of patients also reported cough on direct questioning, which reinforces the importance of active case-finding among patients presenting to health facilities.

In this study restricting screening to those with a cough for 2 weeks or longer would have resulted in failure to detect one-fifth of the confirmed cases. In an Ethiopian study in a high tuberculosis and HIV burden area, tuberculosis in patients with a short cough duration (1 to 3 weeks) was associated one or more of the following: weight loss; absence of response to a short course of antibiotics; and/or living in overcrowded place.[97] Thirty-five percent of such patients had tuberculosis. Teklu et al[98] noted that more than 5% of tuberculosis cases seen at a chest clinic have respiratory symptoms < 2 weeks with cough being the most common presenting complaint. The validation study reported in this thesis confirms that in high tuberculosis prevalence settings, there should be a high index of suspicion of tuberculosis in all patients with cough, even in those reporting a shorter duration of cough.

9.3.6.2 Clinical features predictive of suspected tuberculosis

The symptoms included in the PALSA algorithm (namely, night sweats, loss of weight, and pleuritic chest pain) were shown in multivariable logistic regression analysis to be predictive of suspected and diagnosed tuberculosis. Interestingly, the absence of breathlessness best predicted suspected tuberculosis. Other than cough, the presence of haemoptysis, weight loss, pleuritic chest pain best predicted tuberculosis. Many studies confirm that cough, weight loss, night sweats, and haemoptysis are most commonly associated with tuberculosis.[99 100 101 102]

Identification of predictors of tuberculosis in patients with smear-negative tuberculosis is also important, as making diagnoses in these patients is often difficult.[103] In two studies, cough and sputum production,[104] and cough alone[101] were shown to be the only significant predictors of smear-positive tuberculosis when

compared to smear-negative tuberculosis, respectively. Although additional studies show that absence of cough is associated with smear-negative tuberculosis,[103] others report that cough with or without sputum production is a commonly associated symptom in smear-negative patients with or without HIV infection.[105 104]

9.3.7 Accuracy of the guideline in diagnosing respiratory tract infections

The guideline's poor performance in diagnosing LRTI is of concern since this condition is an important cause of morbidity and mortality in primary care. It performed well in excluding patients who do not have a LRTI, but had a low sensitivity, meaning that many patients who required an antibiotic failed to receive one. The most common incorrect diagnoses were acute exacerbations of asthma or COPD, upper respiratory tract conditions and suspected tuberculosis. While suspecting tuberculosis is a reasonable alternative, and likely to increase detection of active TB, it may result in delayed antibiotic treatment. On the other hand, the requirement for two sputa to be examined in suspected TB would mean that patients would re-attend on two successive days, providing a further opportunity for the diagnosis to be corrected. In addition, the guideline makes provision for an empiric 'trial' of amoxycillin in symptomatic sputum-negative patients, meaning that many patients with suspected TB would have been adequately treated. In addition, many patients may well have presented with viral conditions and might have recovered spontaneously.

9.3.7.1 Clinical predictors of LRTI

In this study, features predictive of LRTI are cough, reported fever, sputum production, dyspnoea, no obstructive airways disease and no wheezing. Assessment of the type of LRTI each patient had (eg. bronchitis, pneumonia) was however not possible, as no definitive investigations were made to determine the underlying cause. Very few patients with severe LRTI were included and most patients had mild acute bronchitic illnesses, therefore the prediction model can be speculated to be more useful in distinguishing between upper and lower respiratory tract conditions, than in

aiding in the diagnosis of pneumonia for example. Systematic recording of chest radiograph abnormalities by the physicians were not done, therefore assessments of which of the patients with LRTI diagnoses had radiographic infiltrates. This can de done as a post-hoc analysis. A review of the clinical features that best predict LRTI concluded that no individual or combinations of symptoms and sign predicted LRTI, and that chest radiography be considered in the event of diagnostic uncertainty.[106]

A number of severity scores have been developed to predict the clinical outcome of patients with community-acquired pneumonia,[107 108 109] but their application in other settings such as primary care in resource limited areas requires prospective validation.[110] Many of these scores require the undertaking of investigations not available to most nurses (for example, chest radiography, blood testing). The CURB[108] and CURB-65,[109] on which the PALSA guideline's management of patients at high risk of severe disease from pneumonia is modelled, contain 4 clinical features that are easily measurable by nurses (confusion of new onset, respiratory rate of $\geq$ 30/min, and systolic or diastolic blood pressures of $<$ 90 and $\leq$ 60, respectively). The CURB-65, adds the variable of age $\geq$ 65 years to the score. Although blood pressure measurement by the nurse was not included in the PALSA guideline, it was included in the data collection form and thus also in the analysis. None of the severity predictors included in the guideline significantly predicted LRTI in this study population. This is most likely a reflection of the definition of LRTI used for analysis (i.e. the lack of a definitive gold standard) and of the large number of patients with milder disease clinically.

Because of the small numbers of patients diagnosed with upper respiratory tract infections, detailed analysis was not possible. In comparison to the PAL multi-country survey, much smaller numbers of patients were seen in this study. This could be attributed to health care utilization patterns in poorer communities in South Africa whereby patients with mild URTIs do not present to busy primary care clinics because of long waiting hours. The latter is however merely speculative. Future guideline revisions will continue to incorporate URTIs, but an attempt will be made to condense these conditions to comprise a smaller section of the guideline.

9.4 STRENGTHS AND LIMITATIONS OF THE VALIDATION STUDY

Diagnostic accuracy studies are important to determine how well the results of a test agree with that of the reference standard.[111] However, a number of factors influence the internal and external validity of the results. Below these factors will be evaluated in the light of the validation study.

9.4.1 Strengths

Study design and study population factors, such as demographic features, disease severity, disease prevalence, and selection of participants can affect the outcome of diagnostic accuracy studies in one of two ways. First, they are potential sources of variations in the study's estimates of the test performance, and second, they can influence the generalisability its findings.[111] Thus, one of the main strengths of the validation study's design is that the index test (the guideline in the hands of the nurse) was evaluated prospectively using consecutive patients. This design reduces bias resulting from under- or over estimation of disease. Additionally, the study patients closely represent the same population to whom the guideline will be applied, and the primary care clinic represents the setting in which it will be tested. These factors provides the same level of diagnostic uncertainty as would be expected in real-life clinical practice.[25]

Another strength of the study is that the eligibility criteria were broad (subjects aged ≥ 15 years with cough or difficult breathing), thereby reducing spectrum bias.[112] Potential for spectrum bias was further reduced by the wide range of diseases and disease severities seen in this study, as sensitivity measures are often higher in studies with a larger proportion of patients with severe disease. These broad inclusion criteria do however have the potential to increase the likelihood of false-positive and false-negative diagnoses due to the larger number of patients with milder disease and co-morbidity.[112 113] Test bias (when the result of the reference standard is known when interpreting the test result) and diagnostic review bias (when the results of the test are

known when interpreting the reference standard) were reduced by blinding of investigators to each others' diagnoses.[114] The reference standard in this study was relatively robust and appropriate – a blinded specialist physician with full access to clinical features and diagnostic tests - which according to Bossuyt et al[115] is defined as the 'best available method for establishing the presence or absence of the condition of interest'. The reference standard was in fact a composite measure of clinical judgment informed by a number of tests. Another strength is that the primary care physician saw the patient immediately after the nurse did, and no treatment was applied in the time between the nurse and the primary care physician seeing the patient. These features reduce both disease progression and treatment paradox biases, respectively.

9.4.2. Limitations

One of the main factors limiting the study's generalisability was that although patients represented a wide clinical spectrum, they were from one clinic, and were seen by only one nurse, 2 primary care physicians, and 2 respiratory physicians. Inclusion of more clinics and investigators may well have resulted in different results. The generablisability of guideline's use by different nurses is better tested in a pragmatic randomised controlled design, such as that performed by in the Free State province and reported above.[1]

9.4.2.1 Limitations arising from patient selection

Patients were recruited primarily from the clinic triage area, and less frequently from the emergency room. Due to limited study staff, only a maximum of ten patients could usually be seen by each investigator every day, and this meant that sampling mostly occurred during the first half of the day. Patients presenting with more severe disease to the emergency room, or those presenting at times when active recruitment did not occur could therefore potentially have been missed.

9.4.2.2 Limitations due to patient-related factors

Interpretation of the questions asked of the patients, or of the answers received by the investigators could have been incorrect, misunderstood or misinterpreted, leading to incorrect recording of information. An important potential reporting bias could relate to the information gained on cannabis use, as cannabis smoking is illegal in South Africa. It is therefore possible that many patients may have under-reported its use.

9.4.2.3 Limitations due to nurse-related factors

Testing of the guideline relied on the skills and interpretation of the nurse, which could have resulted in biasing of results (under-or over-reporting of PALSA diagnoses). She was however instructed to strictly adhere to the guideline. But use of her clinical judgment as influenced by features not included in the PALSA guideline cannot be excluded. As mentioned before, another important potential source of bias was the involvement of only used one nurse. Calculating inter-observer variability was therefore not possible. An important limitation was that intra-observer variability testing was not conducted in this study. Errors in the application of the guideline by the nurse, or in the interpretation of the results could have had a major influence on the estimates of the tests performance. However this study, being pragmatic in nature, aimed to assess the application of the guideline by a nurse working in primary care, and this was achieved. The use of only one nurse could have possibly reduced the impact of variability introduced by different guideline users, as it was the diagnostic accuracy of the guideline rather than the performance of the nurse that was under study. Prior knowledge of respiratory disease could have biased the nurse to favour those diagnoses over different ones.

9.4.2.4 Limitations due to primary care physician-related factors

Systematic errors in the taking of the clinical history and examination of the patient, and the execution of the spirometric measurements could have resulted in information bias in the primary care physicians' recording and interpretation of information. Intra-

and inter-observer variability was not tested for between them, thereby influencing the reliability of the clinical information presented to the respiratory physician. Another important source of bias relates to the reference standard for tuberculosis. Data reporting which medications patients use have not been reported in this study. This information was made available to the respiratory physician, who performed lung function testing on all patients irrespective of their treatment status and current use of medications. The use of inhaled bronchodilator before spirometric testing may have biased the results and resulted in under-detection of reversible airways disease as have been discussed above.

9.4.2.5 Limitations due to respiratory physician-related factors

An important limitation of the validation study was that the respiratory physician did not examine the patients in person, but were provided with clinical information instead. Once again, this situation was unavoidable as the costs and practicalities of employing a specialist physician to participate in a study such as this one was not feasible. The availability of clinical information could be perceived to bias the findings of spirometry and chest radiography. It was the intention of the investigators to provide the respiratory physician with as much clinical information as possible so that the final composite diagnosis reflected usual clinical practice. Of course, under- and over-diagnoses of these respiratory conditions cannot be excluded as further supplementary investigations, such as bronchial hyper-responsiveness testing, skin prick testing, serum IgE testing, and sputum or blood cultures, were not conducted. The reference standards used to diagnose obstructive airways disease were based on the clinical judgement of the respiratory physician. Re-categorisation of the GOLD and GINA guideline definitions could have under-or-over-estimated the number of patients with these conditions. Reliance on clinical judgement to determine other causes of respiratory disease may have also contributed to the reference standard not being robust. However, in the clinical setting in which this pragmatic study was conducted, the physicians' diagnoses were considered feasible. Because this was a cross-sectional study, patients were not followed up to determine the accuracy of the physician or nurse diagnoses for purposes of diagnosis for this study.

9.4.2.6 Limitations due to the use due to the reference standard for tuberculosis

For the investigation of tuberculosis, only those suspected by the primary care physician were investigated by means of sputum examination, thereby introducing partial verification bias. Given the resource availability, testing of all patients in the study was not feasible and therefore bacteriological diagnosis of tuberculosis was used at the reference standard. This study's aim was to examine the performance of the first stage of a 2-stage screening process; the nurse using a guideline (pre-screening) against the generally accepted approach of a primary care physician who has access to sputum testing and a chest radiograph. Bacteriological screening is considered by the author to be the second stage of the screening process. The availability of chest radiography may have been useful in assisting the primary care physician with suspecting tuberculosis. This is supported by the association of the certainty of diagnosis of the primary care physicians with positive sputum results, suggesting that it is unlikely that those that they viewed as not requiring sputum examination had active tuberculosis. The increased association of radiographic changes with smear-positive tuberculosis has been well described.[116] In further support of the physicians' abilities to correctly identify tuberculosis with the aid of chest radiography are the results of a recent study.[117] In that study chest radiographs as a screening tool for tuberculosis was shown to have a sensitivity of 91% in patients with cough $\geq$ 3weeks and/or haemoptysis. However, in other studies a small percentage of symptomatic patients with normal or atypical chest x-rays have also been shown to have culture positive tuberculosis,[118] [105] [119] [104] and these results are of particular importance in high HIV settings.

9.4.2.7 Limitations related to derivation of the predictors for each disease

Factors that improve the validity of predictors derived using multivariable analysis are[120]: (1) prospective data collection, and (2) deriving the set of predictors (the 'prediction rule') from the population in which it will be applied. In this study, one of the factors limiting the direct application of the prediction rules to other populations is that they have not been prospectively validated in other settings in order to test for

their reproducibility or sensibility (whether is makes clinical sense to the user).[120] To address this the study sample could have been separated into a two sub-populations. The first population could have been used to derive the predictors, and the second, for performing prospective validation. However, a criticism of this approach is that validation of a split sample means that the results may still not be relevant to other populations, and that further testing may therefore be necessary.[120]

9.5 Policy implications of the guideline development and validation study

Given the difficult and fragmented origins and evolution of health care in South Africa, large disparities in the provision and distribution of health care still exists. This, and the essential process of healthcare reform has placed a strain on the already overburdened health care system. Provision of simplified interventions, like the PALSA guideline, that works with, rather than against the system, can therefore be considered to be useful.

The PALSA guideline, its development, and its validation have important policy implications at various levels. The methods used to develop the guideline serve to inform policymakers about current gaps and deficiencies in the health system and in the delivery of health care. As evidenced in this study, in-depth consultation with frontline clinicians, such as the nurses, provided an opportunity for the PALSA team to address a 'policy' barrier (nurse prescribing provisions) which ultimately led to a policy change.

Another example of how the guideline has already affected policy is evidenced by the Free State department's insistence on expanding the PALSA guideline to include anti-retroviral therapy and management of HIV/AIDS patients when national government first proposed the launch of this programme in 2003. The decision to expand the guideline occurred even before the results of the trial were analysed. What this implies is that the intervention clearly targeted a health system need, and on face value was thought to be the best option for implementing integrated care. This is a testament to the programme's success. The expanded guideline, the PALSA Plus guide, now also includes treatment for sexually-transmitted diseases and is being

implemented in the Free State and Western Cape provinces with the revision methods modeling that used during its development. The Western Cape government has recently approached the PALSA Plus team to assist with the development of a chronic disease guideline that will integrate hypertension and diabetes mellitus. Plans have also been proposed by the National Department of Health to roll the intervention out nationally, and the guidelines are currently being revised to include nurse-initiated anti-retroviral therapy in the Free State. Furthermore, the training strategy has been modified based on qualitative work done to evaluate its impact on nurse trainers. The underlying principles are the same as that reported in this thesis, but it has been expanded to more explicitly incorporate adult education techniques.

The South African Tuberculosis Control programme welcomed the request by the PALSA Plus team to revise the existing tuberculosis algorithm to include the management of smear-negative tuberculosis and to integrate the diagnosis of tuberculosis with the diagnosis and management of HIV and AIDS. These algorithms have already been revised in collaboration with the Western Cape Department of Health and the University of Cape Town, and have been endorsed for use in both provinces. More barriers research work and evaluation by means of a pragmatic randomised controlled trial are ongoing to inform the further development and implementation of these guidelines.

9.6 Priorities for future research

The results of the validation study will be circulated to relevant role-players, stakeholders, and policymakers. Given the paucity of research in the area of guideline development, adaptation, and validation in developing countries the results of this study will be submitted for publication in peer reviewed journals. One such study has already been accepted for publication.[121] These results will be particularly informative for the implementation of the PAL initiative in other countries.

Clearly, more work in the area of diagnosis of respiratory disease based on clinical findings need to be done. The predictors derived for each disease need to be validated in another population and setting. The weaknesses identified in this study will need to

be addressed in order to increase the validity and generalisability of its findings should future research in this area be undertaken.

9.7 Conclusion

This study shows that a locally-adapted integrated syndromic guideline, tailored to suit local practices and needs is an acceptable and feasible strategy for improving nurse practitioner care in frontline facilities in South Africa. This study also shows that it is possible to develop a valid guideline for use in resource primary care settings, through inter-professional consultation and assessment of local circumstances. The PALSA guideline development and validation studies, as well as the chosen implementation and evaluation strategies can be considered to be a model for development of integrated syndromic guidelines in other developing countries.

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Appendices

Appendix 1: Map of South Africa (Available from: http://www.linx.co.za/provinces [cited 2006 Aug])

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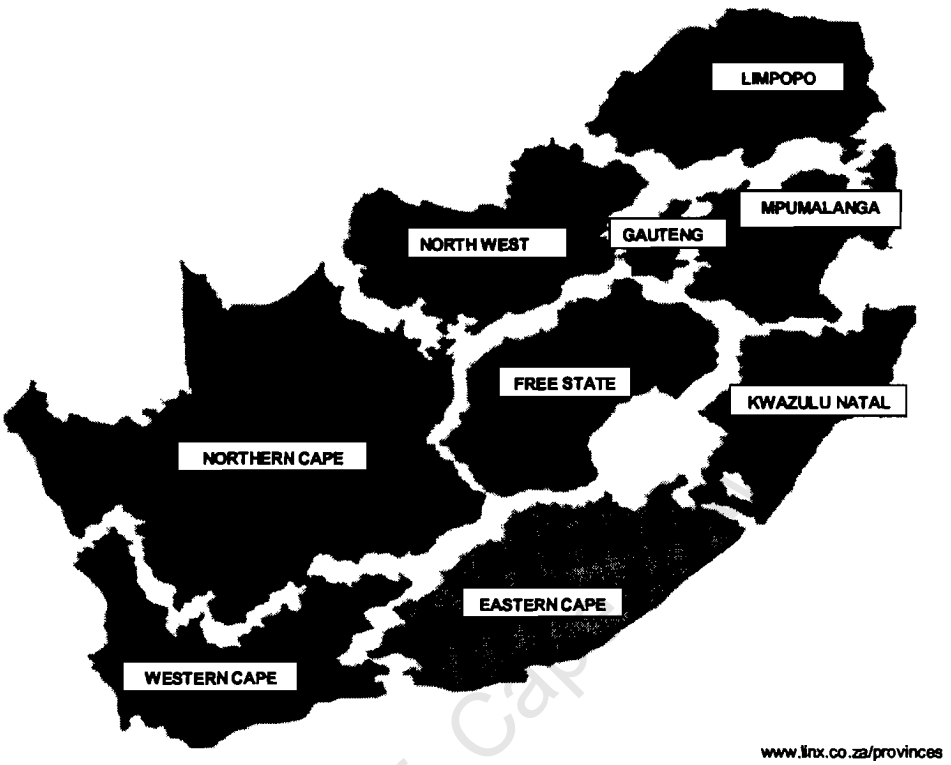
Appendix 1: Map of South Africa (Available from: http://www.linx.co.za/provinces [cited 2006 Aug]) Adapted by author for this thesis.

Map of SA provinces



Appendix 2: The PAL guideline (index, and pages 3-6)

Acute and Chronic Care of the Sick Older Child/Adolescent/Adult with Cough or Difficult Breathing or Fever- For Health Workers in First-Level (Outpatient) Facilities

ASSESS

ASK: WHAT IS YOUR PROBLEM?

Why did you come for this consultation?

- Respond to volunteered or observed problems:
- Ask all patients whether they have cough.
- Determine if patient has acute illness or is here for follow-up.
  - If follow-up of acute illness see p. 9.

Ask if the patient has cough or difficult breathing:

ASK:	*LOOK, LISTEN (all patients)*
• How long have you been coughing? • How long have you had difficult breathing? • Are you having chest pain? If yes, is it new? Severe? Describe it. • How old are you? • If woman of childbearing age, are you pregnant? • Are you coughing up blood (hemoptysis)? If yes, how much? • Do you smoke? If yes, have you lost weight recently? • Do you have asthma,* COPD,* heart failure,* TB? If yes: • Do you have your treatment card? • What medications have you taken in the previous 24 hours? If no: • Have you had previous episodes of cough or difficult breathing? If yes: — Do these episodes of cough or difficult breathing wake you up at night or in the early morning? — Do these episodes occur with exercise? * *Look in Chronic Disease Register*	• Look at the patient's neurological condition. Is the patient: — Lethargic? — Confused? — Agitated? Check respiratory function • Count the breaths in one minute • Look for breathlessness. If present, ask then observe when patient experiences it: —At rest —Talking —Walking - Is patient uncomfortable lying down? • Look for use of accessory muscles • Listen to speech. Is patient: - Not able to speak - Speaks in single words only - Speaks in phrases - Speaks in full sentences • Look/listen for wheezing • Measure temperature • Check if able to walk unaided If patient cannot walk, has neurological signs or appears ill, also:
If KNOWN COPD, ALSO ASK: • Has sputum increased? • Has sputum color changed to yellow or green?	• Look for oedema of both ankles.

AGE	FAST BREATHING IS:	VERY FAST BREATHING IS:
5-12 years	• 30 breaths per minute or more	• 40 breaths per minute or more
13 years or more	• 25 breaths per minute or more	• 30 breaths per minute or more

If no known COPD

Classify in all

CLASSIFY

IDENTIFY TREATMENT

If wheezing — FOR ANY PATIENT WITH WHEEZING
(Asthma or COPD with wheezing or any other disease with wheezing):

- Manage wheezing first using guidelines on Page 6.
- Then also classify and treat using one of these classification tables:

SIGNS:	CLASSIFY AS:	TREATMENTS:
One or more of the following signs: • Very fast breathing or • Very high fever (40°C or above) or • Temperature less than 35°C or • Heart rate 125 beats or more or • Systolic BP less than 90 or • Confusion, agitation or lethargy associated with breathlessness or • Not able to walk unaided or • Uses accessory muscles or • Speaks only in single words or not at all or • Hemoptysis more than 50 ml or • Severe chest pain	SEVERE PNEUMONIA OR VERY SEVERE DISEASE	➢ ***Give first dose IM antibiotics*** ➢ ***Give oxygen*** ➢ ***Position*** ➢ ***Refer urgently to hospital***
Two of the following signs: • Fast breathing • Fever (37.5°C or above) • Pleuritic chest pain	PNEUMONIA	➢ Give appropriate oral antibiotics. ***Exception: if second/third trimester pregnancy, give first dose IM antibiotics and refer urgently to hospital.*** ➢ If smoking, counsel to stop smoking ➢ Advise when to return immediately ➢ Follow-up in 2 days
• Cough or difficult breathing for more than 3 weeks or • Weight loss and bloody sputum in smoker or • Recurrent episodes of cough or difficult breathing which: – Wake patient at night or in the early morning or – Occur with exercise	POSSIBLE CHRONIC LUNG PROBLEM	➢ Refer to district hospital for assessment if a chronic lung problem has not been diagnosed If cough more than 2 weeks, send 3 sputums for TB or send the patient to district hospital for sputum testing (record in register– p. 10). (If sputums sent before, check register for result.) ➢ If smoking, counsel to stop smoking.
• Insufficient signs for the above classifications	NO PNEUMONIA-COUGH/ COLD, OR BRONCHITIS	➢ Advise to use safe, soothing remedy. ➢ If smoking, counsel to stop smoking.

	SIGNS:	CLASSIFY AS:	TREATMENTS:
If known COPD	One or more of the following signs: NEW or WORSE: • Very fast breathing or • Confusion, agitation or lethargy associated with breathlessness or • Not able to walk unaided or • Temperature less than 35°C or • Oedema of both ankles or • Speaks only in single words or not at all or • Hemoptysis more than 50 ml or	**COPD** with SEVERE DETERIOR-ATION**	➢ ***Give appropriate IM antibiotics*** ➢ ***Give oxygen*** ➢ ***Refer urgently to hospital with oxygen****
	• Increased sputum production or • Sputum color becomes yellow or green (color change) or • Fever (37.5°C or above)	**ACUTE INFECTION in COPD****	➢ Give appropriate oral antibiotics ➢ Give routine follow-up care for known COPD (check regimen, compliance with treatment plan from hospital. See p. 34.) If no treatment card for COPD, refer to hospital for evaluation. ➢ If smoking, counsel to stop smoking. ➢ Follow-up in 1 week
	• None of the above	**'STABLE' COPD****	➢ No new treatment ➢ If smoking, counsel to stop smoking. ➢ Give routine follow-up care for known COPD (check regimen, compliance with treatment plan from hospital. See p. 34) If no treatment card for COPD, refer to hospital for

* *Unless end-stage COPD and family prefers palliation at home (see p.47).*

** *COPD includes medical diagnoses of emphysema and chronic bronchitis. COPD management is also appropriate for bronchiectasis.*

CLASSIFY SEVERITY OF WHEEZING AND TREAT URGENTLY

Classify if wheezing

Patient may have asthma, COPD or any wheezing

SIGNS:	CLASSIFY AS:	TREATMENTS:
One or more of the following signs: • Breathless at rest or • Speaks in single words or not at all or • Confusion, agitation, or lethargy associated with any breathlessness	SEVERE WHEEZING	➢ ***Immediately give inhaled salbutamol*** — ***Exception: if severe respiratory distress, give 20 puffs salbutamol in a row or give continuously by nebulizer with oxygen. If no response in 10 minutes, give epinephrine.*** ➢ ***Give oxygen*** ➢ ***Position for greatest ease in breathing*** ➢ ***Immediately prepare for urgent referral to hospital with oxygen and salbutamol**** ➢ ***Repeat inhaled salbutamol every 10 minutes.*** ➢ ***Give prednisone*** ➢ ***If fever, give IM antibiotic*** ➢ ***Refer urgently to hospital with***
• Breathless on talking or • Uncomfortable lying down or • Speaks only in phrases or • Uses accessory muscles	MODERATE WHEEZING	➢ Immediately give inhaled salbutamol. Repeat every 10 minutes if still breathless or wheezing. ➢ Give oxygen ➢ Give prednisone if known asthma or COPD and prednisone is in treatment plan (from hospital).
All of the following signs: • Breathless only on walking (or not breathless) and • Comfortable lying down and • Speaks in full sentences	MILD WHEEZING	➢ Immediately give inhaled salbutamol. Repeat every 20 minutes if still breathless or wheezing.

For MILD or MODERATE WHEEZING, at one hour after treatment, reassess respiratory function and reclassify severity of wheezing.

Then also classify using either the pneumonia table (p. 4) or COPD table (p. 5).

* Unless end-stage COPD and family prefers palliation at home.

RECLASSIFY SEVERITY OF WHEEZING ONE HOUR AFTER TREATMENT

SIGNS:	CLASSIFY AS:	TREATMENTS:
One or more of the following signs: • Breathless at rest or • Speaks in single words or not at all or • Confusion, agitation, or lethargy associated with any breathlessness	SEVERE WHEEZING	➢ ***Give prednisone*** ➢ ***If fever, give IM antibiotic*** ➢ ***Position for greatest ease in breathing*** ➢ ***Refer urgently to hospital with oxygen**** ➢ ***Continue inhaled salbutamol en route***
• Breathless on talking or • Uncomfortable lying down or • Speaks only in phrases or • Uses accessory muscles	MODERATE WHEEZING	➢ ***Give prednisone if known asthma or COPD and prednisone is in treatment plan (from hospital)*** ➢ ***If fever, give oral or IM antibiotic*** ➢ ***Refer urgently to hospital with oxygen**** ➢ ***Continue inhaled salbutamol en route***
All of the following signs: • Breathless only on walking (or not breathless) and • Comfortable lying down and • Speaks in full sentences	MILD WHEEZING	➢ Treat at home. ➢ If previous assessment was moderate or patient has been breathless for more than 1 week, arrange for non-urgent referral to hospital*. ➢ If known asthma or COPD, consider recent symptoms and adjust treatment (p. 20 or 34). Refer for reevaluation of treatment plan if needed (within 1 week). ➢ If patient not known to have asthma or COPD with wheezing, refer for assessment (see in follow up in 1-2 days if this is delayed). Teach patient to use metered-dose inhaler at home and continue inhaled salbutamol up to every 3 to 6 hours as needed. ➢ If smoking, counsel to stop smoking. ➢ Advise when to return immediately.

Appendix 3: List of Cochrane reviews (Dated till 2002/3)

LIST OF COCHRANE REVIEWS

Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. Cochrane Database of Systematic Reviews: Reviews 2000 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD002742

Graham V, Lasserson TJ, Rowe BH. Antibiotics for acute asthma. Cochrane Database of Systematic Reviews: Reviews 2001 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD002741

Adams N, Bestall J, Jones P. Beclomethasone at different doses for chronic asthma. Cochrane Database of Systematic Reviews: Reviews 1999 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD002879

Adams N, Bestall JM, Jones PW. Beclomethasone versus budesonide for chronic asthma. Cochrane Database of Systematic Reviews: Reviews 2000 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003530

Adams N, Bestall J, Jones P. Budesonide at different doses for chronic asthma. Cochrane Database of Systematic Reviews: Reviews 2000 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003271

Adams N, Bestall J, Jones PW. Budesonide versus placebo for chronic asthma in children and adults. Cochrane Database of Systematic Reviews: Reviews 1999 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003274

Ram FSF, Picot J, Campbell D, Kelly KD, Manser R, Wood-Baker R. Combined corticosteroid and longacting bronchodilator in one inhaler for chronic asthma. Cochrane Database of Systematic Reviews: Protocols 2000 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD002998

Camargo CA, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists for acute asthma. Cochrane Database of Systematic Reviews: Reviews 2003 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD001115

Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. Cochrane Database of Systematic Reviews: Reviews 2001 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD001740

Rowe BH, Spooner CH, Ducharme FM, Bretzlaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. Cochrane Database of Systematic Reviews: Reviews 2001 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD000195

Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. Cochrane Database of Systematic Reviews: Reviews 2001 Issue 1 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD002178

Edmonds ML, Camargo CA, Pollack CV, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. Cochrane Database of Systematic Reviews: Reviews 2003 Issue 3 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD002308

Sharpe HM, Sin D, Kaufman BJ, Spooner CH, Rowe BH. Education interventions for adults who attend the emergency room for acute asthma. Cochrane Database of Systematic Reviews: Protocols 2001 Issue 2 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD003000

Wolf FM, Grum CM, Clark NM. Educational interventions for asthma in adults. Cochrane Database of Systematic Reviews: Protocols 1996 Issue 4 John Wiley & Sons, Ltd Chichester, UK DOI: 10.1002/14651858.CD000325

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Appendix 4: Statistics tables used to calculate the sample size

TABLES USED FOR STATISTICAL PLAN PRIOR TO CONDUCTING THE PALSA VALIDATION STUDY

The sample size refers to (for sensitivity) the number of positive patients according to the gold standard test or (for specificity) the number of negative cases on gold standard.

- For positive predictive values, sample size refers to the number with a positive screening test
- For negative predictive values, sample size refers to the number with a negative screening test

Alpha = 0.05; Power=90%

Hypothesised true sensitivity (or specificity or PPV or NPV)	You want (estimate-true value) to be no more than the following proportion		
	0.05	0.10	0.20
0.05	264	79	25
0.10	438	122	35
0.20	718	189	50
0.30	912	233	60
0.40	1022	257	64
0.50	1047	259	62
0.60	988	240	55
0.70	845	200	42
0.80	617	137	16
0.90	301	35	
0.95	73		

Sample size needed for single sample to estimate sensitivity (or specificity)

Confidence level, 1-alpha	0.95	0.95	0.95	0.95	0.95
1 or 2 sided interval?	2	2	2	2	2
Proportion successes, P	0.15	0.1	0.05	0.1	0.05
Agreement, Kappa	0.6	0.6	0.6	0.6	0.6
Distance from Kappa to limit, L	0.05	0.05	0.05	0.1	0.1
n sample size	1976	2820	5386	705	1347

Appendix 5: The PALSA guideline

PRACTICAL APPROACH TO LUNG HEALTH IN SOUTH AFRICA (PALSA) GUIDELINES

First-Level Primary Care Management of Respiratory Diseases

Approach to the adult patient who presents with difficult breathing and/or cough.

CONTENTS

CLASSIFY ACCORDING TO SYMPTOMS

Cough AND/OR
Difficult breathing (defined as breathlessness at rest or on activity, wheeze and/or tight chest)

ASK ABOUT, AND RECORD

- Name
- Age
- Medical history
- Presenting symptoms
- Purpose of the visit

If the purpose of this visit is to treat and assess:
- Worsening of symptoms or
- New symptoms

If unsure of diagnosis

If continued treatment of known lung disease with:
- No worsening of symptoms
- No new symptoms
- No uncertainty about diagnosis

Symptoms present < 2 weeks

Go to page 2

Symptoms present ≥ 2 weeks

Cough with or without sputum production

Exclude TB
(Go to page 16)
Consider **Chronic Bronchitis**
(Go to page 15)

Cough and difficult breathing

Exclude TB
(Go to page 16)
Consider **Asthma or COPD**
(Go to page 12)

Difficult breathing alone

- **Asthma** (Go to page 13)
- **COPD** (Go to page 14)
- **TB** (Go to page 16)
- **HIV/AIDS** (Go to page 20)

SYMPTOMS < 2 WEEKS: ASSESSMENT AND INITIAL MANAGEMENT

IF ONE OR MORE SYMPTOMS PRESENT, ASSESS SEVERITY

	SEVERE	MILD
BREATHLESSNESS	At rest or while talking	While walking
MENTAL STATE	May be agitated or confused	
USE OF BREATHING MUSCLES	Prominent	May be normal
BREATH RATE	≥ 30 per minute	20 - 29 per minute
HEART RATE	≥ 120 per minute	100-119 per minute
HAEMOPTYSIS	½ Tablespoon of frank blood	Blood streaking

INITIAL MANAGEMENT OF SEVERE PATIENTS

Airway: Position for greatest ease of breathing.
Breathing: 40% Face-mask oxygen or at 4 L/min via nasal prongs.
Call ambulance.
Doctor: Phone or refer.
Extra emergency treatment:

Wheezing or light chest

SEVERE ACUTE ASTHMA/COPD EXACERBATIONS

4-8 puffs beta-agonist via spacer every 20 minutes in the first hour, then hourly depending on response

OR

Nebulised beta-agonist every 20 minutes, then hourly depending on response

Oral prednisone 40mg

Temperature ≥ 38 °C

SEVERE LOWER RESPIRATORY TRACT INFECTION

Amoxycillin
If penicillin allergic:
Cotrimoxazole 960 mg

ASK, LISTEN:

Wheezing, tight chest?

Most likely **asthma** or **chronic obstructive airways disease (COPD) exacerbation.**

Go to page 3

ASK, MEASURE:

Fever and/or pain on breathing or coughing and/or sputum production

Most likely **LRTI, TB** or **suppurative lung disease.**

Go to page 7

ASK, LOOK:

Runny nose
Sore throat
Pain and/or tenderness over sinuses
Ear problem

UPPER RESPIRATORY TRACT INFECTION

Go to page 8-11

FURTHER TREATMENT OF THE WHEEZING PATIENT: ACUTE ASTHMA/COPD EXACERBATION

- 4 puffs beta-agonist via spacer every 20 minutes for one hour then reassess.

OR

Nebulise using beta-agonist every 20 minutes for one hour then reassess.

- Give 1 dose of oral prednisone 40 mg stat.

REASSESS SYMPTOMS AFTER 1 HOUR

BETTER OR NO SYMPTOMS	NO CHANGE	WORSE
OBSERVE FOR ONE MORE HOUR, THEN FOLLOW DISCHARGE PLAN ON PAGE 4	**REPEAT ABOVE TREATMENT AND ASSESS WITHIN ONE HOUR** If worsening of symptoms, treat as severe and refer. If no response within two hours, refer.	**FOLLOW TREATMENT PLAN FOR SEVERE PATIENT ON PAGE 2.**

DISCHARGE PLAN FOR THE WHEEZING PATIENT WHO HAS RESPONDED TO TREATMENT

- Increase the dose and frequency of the inhaled bronchodilator to a maximum of 2 puffs 4 times a day.
- If the patient is already on inhaled corticosteroids: check compliance (are medications taken twice a day, every day)
  : check inhaler technique (are the inhalers used correctly)
- If poor compliance and/or technique instruct patient on correct drug usage.
- Give 40mg of prednisone orally (once daily) for 7 days to patients with the following:
  - History of recent emergency visits for asthma.
  - Worsening of asthma symptoms in the months or weeks prior the onset of the acute attack.
  - History of previous hospital or intensive care unit admission for asthma.
- If the patient reports a cough with new or increased sputum production and/or change in sputum colour (yellow, green) and/or fever, add Amoxycillin 500mg three times a day for 7 days OR if penicillin-allergic, Erythromycin 500mg four times a day for 7 days.
- If the underlying lung condition is unknown, go to page 12 to make diagnosis.
- Encourage all patients to stop smoking cigarettes, pipes or dagga.
- Book follow-up visit before medicines are expected to run out.

TELL PATIENT TO RETURN IF:

- Symptoms get worse.
- Not better after a course of oral prednisone has been completed.

FURTHER TREATMENT OF THE PATIENT WITH FEVER AND/OR PAIN ON BREATHING OR COUGHING: LOWER RESPIRATORY TRACT INFECTION

IS THIS PATIENT AT HIGH RISK OF SEVERE RESPIRATORY INFECTION?

- ≥ 60 years old
- Frail with suspected AIDS
- Known: Lung disease
  Heart disease
  Liver disease
  Diabetes Mellitus

Immediately give 1 gram Amoxycillin orally
OR
If penicillin-allergic, Erythromycin 500mg orally
AND
REFER TO NEXT LEVEL FACILITY OR CLINIC DOCTOR

NOT AT HIGH RISK OF SEVERE RESPIRATORY INFECTION?

- Bed rest at home
- Encourage high fluid intake
- No smoking
- Treat pain and fever with paracetamol 1-2 tablets 4 times a day.
- If new or increased sputum production with colour change, prescribe Amoxycillin 500mg orally three times a day for 7 days OR if penicillin-allergic, Erythromycin 500mg orally 6 hourly for 7 days.
- Look for signs of HIV/AIDS (Go to page 20)
- **Ask about symptoms of TB** (such as loss of weight, night sweats) (Go to page 16)

Refer if:
- Getting worse, or no response.
- Still not completely better within 7 days.

MILDLY ILL PATIENT WITH RUNNY/BLOCKED NOSE: RHINITIS

Ask about associated
- Mild sore throat
- Fever

Consider: **Common cold**

REASSURE PATIENT THAT ANTIBIOTICS ARE NOT NECESSARY.

Consider oxymetazoline 0.05% nose drops, 2 drops in each nostril every 6-8 hours for **no longer** than 1 day.

If:
Symptoms on most days for ≥ 4 weeks, ask about
- Sneezing
- Itching

Consider: **Allergic rhinitis (hayfever)**

INTERMITTENT
< 4 days per week

- 0.9% saline nose drops.
- Chlorpheniramine 4mg 3-4 times a day when necessary Beware: Side-effect is sedation.

PERSISTENT
≥ 4 days per week

- 0.9% saline nose drops.
- Chlorpheniramine 4mg 3-4 times a day when necessary Beware: Side-effect is sedation.
- Refer to next level facility for steroid nasal spray.

MILDLY ILL PATIENT WITH PAIN AND/OR TENDERNESS OVER SINUSES: ACUTE SINUSITIS

- Clear nasal discharge.
- Mild pain over sinuses.
- Post-nasal drip.

Consider: **Viral sinusitis**

REASSURE PATIENT THAT ANTIBIOTICS ARE NOT NECESSARY.

- Instruct patient to mix 1/2 teaspoon salt + 1 teaspoon bicarbonate of soda in 500ml lukewarm water. Sniff up each nostril every 4-6 hours.
  OR
  0.9% Sodium chloride drops in each nostril every 4-6 hours.
- Oxymetazoline 0.05% nose drops, 2 drops in each nostril every 6-8 hours for **no longer** than 5 days.
- Paracetamol 1-2 tablets 4 times a day.

- Symptoms ≥ 7 days.
  Severe symptoms regardless of duration.
- Pussy nasal discharge.
- Face or tooth pain and tenderness.

Consider: **Bacterial sinusitis**

- Amoxycillin 500mg orally three times a day for 10 days
  OR
  If penicillin-allergic, give cotrimoxazole (Bactrim) 2 tablets (80/400mg) twice a day for 5 days.
- Instruct patient to mix 1/2 teaspoon salt + 1 teaspoon bicarbonate of soda in 500ml lukewarm water. Sniff up each nostril every 4-6 hours.
  OR
  0.9% Sodium chloride drops in each nostril every 4-6 hours.
- Oxymetazoline 0.05% nose drops, 2 drops in each nostril every 6-8 hours for **no longer** than 5 days.
- Paracetamol 1-2 tablets 4 times a day.

Refer if:
- Tooth abscess suspected.
- Swelling around eye or face.
- Failure to respond to medication after 10 days.

MILDLY ILL PATIENT WITH SORE THROAT: ACUTE PHARYNGITIS, TONSILLITIS, ORAL CANDIDA

RED THROAT WITHOUT PUS

Consider: **Pharyngitis**

REASSURE PATIENT THAT ANTIBIOTICS ARE NOT NECESSARY.

- Salt water mouthwash (1/2 teaspoon salt in a glass of warm water). Gargle twice a day.
- Paracetamol 1-2 tablets 4 times a day.

RED THROAT, WITH PUS OR WHITE PATCHES ON TONSILS

Consider: **Bacterial tonsillitis**

- Salt water mouthwash (1/2 teaspoon salt in a glass of warm water). Gargle twice a day.
- Phenoxymethylpenicillin (Pen VK) 500mg orally every 6 hours for 10 days.

OR

If penicillin-allergic, give Erythromycin 250mg 6 hourly before meals for 10 days.

- Paracetamol 1-2 tablets 4 times a day.

Refer if:

- Severe swallowing problems.
- Inability to open mouth.
- More than 4 documented episodes per year.

WHITE PATCHES ON CHEEKS, GUMS, TONGUE AND PALATE

Consider: **Oral candida (thrush)**

- Nystatin lozenges 100 000 IU - 4 times a day for 10 days.

OR

Nystatin 100 000 IU/ml 1-2 ml 4 times a day for 10 days.

- Exclude HIV infection.
(Go to page 20)

Refer if:

- No response to Nystatin within 5 days. Fluconazole to be prescribed by doctor.
- Extensive disease.
- Recurrent episodes.

Examine the cheeks

Examine the tongue

Examine the palate

MILDLY ILL PATIENT WITH EAR PROBLEM: ACUTE AND CHRONIC EAR PROBLEMS

LOOK IN EAR

OUTER EAR AND EAR CANAL

OTITIS EXTERNA

Inflammation or infection of skin of the outer ear

- Give Flucloxacillin 250mg orally 4 times a day
  OR
  If penicillin-allergic, give Erythromycin stearate 250mg 4 times a day for 5 days.
- Paracetamol 1 - 2 tablets 4 times a day for pain.

Inflammation or infection of ear canal

- Give Flucloxacillin 250mg orally 4 times a day.
  OR
  If penicillin-allergic, give Erythromycin stearate 250mg 4 times a day for 5 days
- 2% Acetic acid in alcohol, 6 hourly for 5 days.
- Dry mop ear.
  (Go to page 11)
- Paracetamol 1 - 2 tablets 4 times a day for pain.

Refer if:
- Diabetic.
- If no response within 48 hrs.

EARDRUM

ACUTE OTITIS MEDIA

Inflamed or bulging eardrum, or pus from ear for < 2 weeks

- Dry mop ear.
  (Go to page 11)
- Amoxycillin 250mg orally three times a day for 5 days.
  OR
  If penicillin-allergic, give Bactrim 2 tablets (80/400mg) twice a day for 5 days.
- Paracetamol 1-2 tablets 4 times a day for pain.

Refer if:
- No response after 5 days.
- Swelling and tenderness of skin behind ear.
- Persistent pain.

CHRONIC

Perforation and pus from ear for > 2 weeks

- The ear can only heal if dry.
- Dry mop ear.
  (Go to page 11)
- Paracetamol 1-2 tablets 4 times a day for pain.

Refer if:
- No improvement after 4 weeks.
- Foul-smelling discharge.
- Large hole in eardrum.
- Hearing loss
- Pain.

Otitis Externa

Inflamed, swollen outer ear

Red swollen ear canal

Acute Otitis Media

Inflamed eardrum

Bulging eardrum

Chronic Otitis Media

Dry perforation

DRY MOPPING THE EAR

Demonstrate method to patient.

- Roll a piece of paper towel into a wick.
- Insert wick into ear and remove once it is wet.
- Repeat 4 times a day until ear is dry.
- Insert acetic acid ear drops if indicated (go to page 10) - 4 drops in affected ear.
- Never leave the wick or any other object inside the ear.

DIAGNOSING OBSTRUCTIVE LUNG DISEASE

It is not always easy to decide whether a patient has asthma or COPD as the symptoms may be similar, or both diseases may be present.
A few questions may help with the diagnosis.

Ask if:

- Symptoms started during childhood or early adulthood.
- History of hayfever, eczema and/or allergies.
- Family history of asthma.
- Symptoms only during attacks with periods of normal breathing in between.
- Symptoms are usually worse: at night; in the early hours of the morning; during an upper respiratory tract infection or when the weather changes.
- Symptoms improve or disappear after using inhaler.

TREAT AS ASTHMA.
REFER TO DOCTOR WITHIN 1 MONTH
Go to page 13

Ask if:

- Symptoms started later in life (usually after the age of 35 years).
- Symptoms slowly worsened over a long period of time.
- Long history of daily or frequent cough and sputum production (usually starts long before the onset of shortness of breath).
- Short of breath for most of the day, rather than at night or during the early hours of the morning only.
- History of heavy smoking eg. more than 20 cigarettes / day for 15 years or more.

TREAT AS COPD.
REFER TO DOCTOR WITHIN 1 MONTH.
Go to page 14

(If unsure, treat as asthma)

If ≤ 1 feature of asthma, and no significant history of smoking, consider a cardiac or non-lung cause of breathlessness, especially if associated hypertension, ischaemic heart disease and/or diabetes mellitus.

MANAGEMENT OF CHRONIC ASTHMA

The aim of asthma management is to obtain complete control of all features of asthma.

Aim for:

1) Minimal (ideally no) daytime and night time symptoms
2) Minimal or no exacerbations (asthma attacks)
3) Minimal need for quick-relief medications
4) No limitations of daily activities

ASSESS CONTROL OF ASTHMA BY ASKING ABOUT DAY AND NIGHT TIME SYMPTOMS

LEVEL OF CONTROL	WELL-CONTROLLED	MODERATE CONTROL	POOR CONTROL
Daytime symptoms per week	<2 times / week	2-4 times / week	Continuous
Night time symptoms per month	<2 times / month	2-4 times /month	Frequent

LEVELS OF TREATMENT	LOW (if well-controlled)	MODERATE (if moderate control)	MAXIMUM (if poor control)
Inhaled salbutamol	2 puffs when needed	2 puffs when needed	2 puffs when needed May be required 4-6 times per day.
Inhaled corticosteroids	200-400 micrograms / day	800 micrograms / day	800-1600 micrograms / day
Slow-release theophylline Doctor to initiate	-	-	1 tablet twice a day
Oral prednisone	-	-	40mg orally (once daily) for 14 days to gain rapid control.

REVIEW EVERY 3 MONTHS

IF COMPLETE CONTROL AT ANY LEVEL OF TREATMENT

- Continue current medication.
- At next visit, reduce treatment to previous level (step-down) if control is still complete.
- Schedule next appointment.

IF POOR CONTROL AT ANY LEVEL OF TREATMENT

- Increase to next level of treatment (step-up).
- Consider adding prednisone 40mg orally once daily for 7 days and reassess in 1 month.

Refer if poor control despite stepping-up.

MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

The aim of COPD management is to:

- Encourage patients to stop smoking in order to prevent worsening of disease.
- Improve symptoms with inhaled bronchodilators.
- Recognise and treat acute exacerbations early.

ENCOURAGE THE PATIENT TO STOP SMOKING

Ask:	Identify and document all tobacco use at each visit.
Advise:	Strongly urge the patient to quit.
Assess:	Determine willingness to make a quit attempt.
Assist:	Help the patient to quit.
Arrange:	Schedule follow-up contact.

	MODERATE	SEVERE	SEVERE COPD WITH COMPLICATIONS	INFECTION
Symptoms	Mild breathlessness on usual activity	Breathlessness on minimal activity or continuously.	Ankle oedema	Increased sputum purulence or colour change to yellow/green
Treatment Options				
Bronchodilators				
Inhaled salbutamol	2 puffs when needed	2 puffs when needed	2 puffs 4 times a day	2 puffs when needed
Inhaled ipratopium bromide	-	2 puffs when needed (up to 4 times per day)	2 puffs 4 times a day	2 puffs when needed (up to 4 times per day)
Theophylline	1 tablet 2 times per day	1 tablet 2 times per day	1 tablet 2 times per day	1 tablet 2 times per day
				Amoxycillin 500mg three times a day for 7 days OR If penicillin-allergic, Erythromycin 500mg four times for 7 days.
				Prednisone 40mg orally (once daily) for 14 days

REVIEW EVERY 3 TO 6 MONTHS

Refer for diuretics if ankle oedema

CHRONIC COUGH WITH OR WITHOUT SPUTUM PRODUCTION; NO BREATHLESSNESS: CHRONIC BRONCHITIS

- **Usually in heavy smokers, or those with lung damage.**
- Daily cough with or without sputum production for months or years.
- Usually begins in middle or old age.
- Heavy occupational (dust, mines, industry) or domestic air pollution (indoor fires or gas stoves) exposure in some.

Treatment

THE MOST EFFECTIVE TREATMENT IS TO REMOVE THE CAUSE!

- All patients should be advised to stop smoking.
- If possible, avoid domestic pollution, occupational exposure and substance abuse (eg. dagga).

Refer:
- If no history of smoking.

DIAGNOSING TUBERCULOSIS (TB)*

SUSPECT TB WHEN:

- Patient reports cough for ≥ 2 weeks.
- Unintentional weight loss.
- Loss of appetite.
- Night sweats and fever.
- Blood-stained sputum.
- Known HIV-positive or AIDS patients.

METHOD OF SPUTUM COLLECTION

Patient:

- Must stand in a well-ventilated room or outside.
- Rinse mouth with water.
- Take a deep breath, and cough forcibly.

Nurse:

- Must not stand in front of patient during the procedure.
- Replace and secure the lid immediately.
- Wash hands after handling specimen.
- Place specimen in bag and store in fridge while awaiting collection.

TB SUSPECTED

NEW, OR PREVIOUSLY CONFIRMED TB TREATED FOR < 4 WEEKS

Test sputum. Label bottles before dispensing them to patients.

Day 1: For Acid-Fast Bacilli (AFB's).

Day 2: Early morning sputum, at home, for AFB's.

PREVIOUS TB TREATED FOR ≥ 4 WEEKS

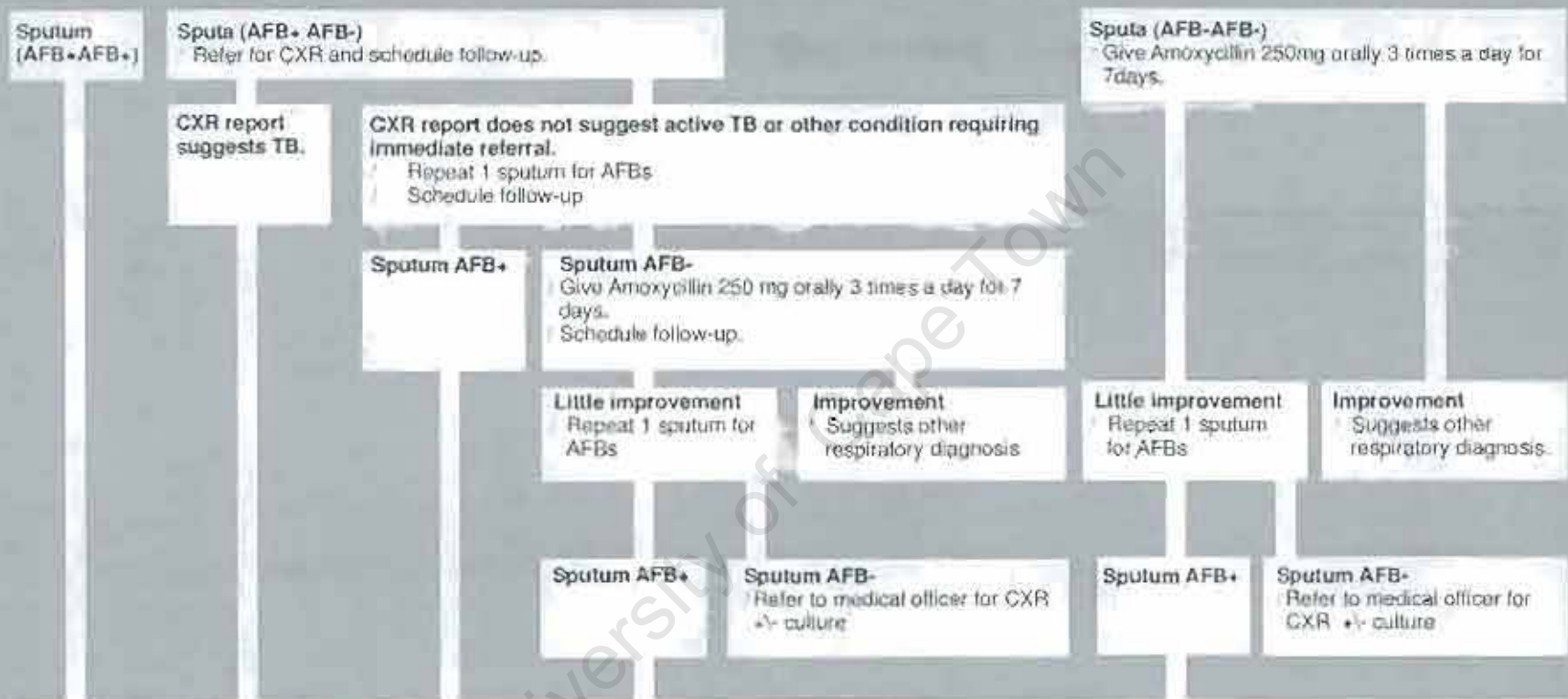
Day 1: For Acid-Fast Bacilli (AFB's).

Day 2: Two early morning sputa, at home.

- 1 for AFB's
- 1 for culture and sensitivity testing.

*According to the South African Tuberculosis Control Practical Guidelines 2000

SPUTUM RESULTS



ACTIVE TB CONFIRMED

- Notify and register patient.
- If new case, or previous confirmed TB treatment for < 4 weeks, register as **NEW CASE: SPUTUM-POSITIVE PULMONARY TB** and start the intensive phase of **REGIMEN 1**. (Go to page 18)
- If previous TB treatment for ≥ 4 weeks, register as **RETREATMENT PATIENT: SPUTUM-POSITIVE PULMONARY TB**, and start the intensive phase of **REGIMEN 2**. (Go to page 19)
- Offer HIV test to all patients. (Go to page 20)
- Select DOT supervisor.

INITIAL TREATMENT FOR REGIMEN ONE

START INTENSIVE PHASE
Rifampicin/Isoniazid/Pyrazinamide/Ethambutol 120/60/300/200mg (given 5 days a week)

< 50 kg	≥ 50 kg
4 tablets	5 tablets

At the end of 2 MONTHS of INTENSIVE treatment, take 2 sputa for AFBs. Schedule follow-up.

Sputa AFB- AFB-

Sputa AFB+ AFB- OR Sputa AFB+ AFB+
- Continue intensive phase for 1 more month.

At the end of 3 MONTHS, repeat 2 sputa for AFBs
- Schedule follow-up.

Sputa AFB- AFB-

Sputa AFB+ AFB- OR Sputa AFB+ AFB+
- Take sputum for culture and sensitivity.
- Schedule follow-up.
- If susceptible, continue. If resistant refer to MDR unit.

START CONTINUATION PHASE

	< 50 kg	≥ 50 kg
Rifampicin/Isoniazid 150/100mg.	3 tablets	-
Rifampicin/Isoniazid 300/150mg.	-	2 tablets

At the end of 5 months of treatment, take 2 sputa for AFBs. Schedule follow-up.

Sputa AFB- AFB- or unable to produce sputum.
- Stop treatment and register as **CURED.**
- Discharge from TB clinic.
- Refer HIV-positive patients to the general clinic for further management.

Sputa AFB+ AFB- OR Sputa AFB+ AFB+
- Register as **TREATMENT FAILURE.**
- Take sputum for culture and sensitivity
- Re-register as a **RETREATMENT** patient, and refer to follow-up plan for Regimen 2.

TREATMENT PLAN FOR REGIMEN TWO

START INTENSIVE PHASE	< 50 kg	≥ 50 kg
Rifampicin/Isoniazid/Pyrazinamide/Ethambutol 120/60/300/200mg (given 5 days a week) PLUS	4 tablets	5 tablets
Streptomycin (given 5 days a week) intramuscularly.	750mg	1000mg
THIRD MONTH		
Rifampicin/Isoniazid/Pyrazinamide/Ethambutol 120/60/300/200mg (given 5 days a week) ONLY	4 tablets	5 tablets

At 6 weeks review the susceptibility results of the initial sputum. If:

Susceptible
- Continue treatment

Resistant
- Refer to MDR unit

At the end of 3 months, repeat 2 sputa for AFBs
- Schedule follow-up

Sputa AFB- AFB-

Sputa AFB+ AFB- OR Sputa AFB+ AFB+
- Repeat sputum for culture and sensitivity
- Schedule follow-up
- If susceptible, continue. If resistant refer to MDR unit.

START CONTINUATION PHASE	< 50 kg	≥ 50 kg
Rifampicin/Isoniazid 150/100mg + Ethambutol 400mg	3 tablets + 2 tablets	-
Rifampicin/Isoniazid 300/150mg + Ethambutol 400mg	-	2 tablets + 3 tablets

At the end of 7 months of treatment, take 2 sputa for AFBs. Schedule follow-up.

Sputa AFB- AFB- or unable to produce sputum.
- Stop treatment and register as **CURED.**
- Discharge from TB clinic.
- Refer HIV-positive patients to the general clinic for management.

Sputa AFB+ AFB- OR Sputa AFB+ AFB+
- Register as **TREATMENT FAILURE.**
- Take sputum for culture and sensitivity.
- Refer to MDR unit.

HIV/AIDS
SUSPECT HIV/AIDS IN ALL WITH THE FOLLOWING:

- TB
- Recurrent respiratory infections
- Mouth lesions eg. Oral candida
- Skin infections eg. Herpes Zoster
- Severe weight loss
- Unexplained fever for > 4 weeks
- Sexually transmitted infections
- Painless swollen glands
- Long history of diarrhoea
- History of engaging in high-risk behaviour (eg. Vaginal, anal or oral sex without a condom)

LOOK FOR

- White patches in the mouth, which are scratched off with difficulty, causing bleeding **(ORAL THRUSH/CANDIDA).**
- Painful rash with blisters, confined to one part of the body **(HERPES ZOSTER).**
- Bluish-black patches or lumps on skin or mouth **(KAPOSI'S SARCOMA).**
- Evidence of severe loss of weight.
- Genital ulcers or discharge.

- **DO YOU SUSPECT HIV/AIDS ?**
- **DOES THE PATIENT REQUEST AN HIV TEST?**

INFORM ABOUT VOLUNTARY CONFIDENTIAL COUNSELLING AND TESTING (VCCT)

Educate patient about HIV/AIDS, methods of transmission and risk factors
Explain about VCCT:

- Who will perform the counselling and the testing.
- That it is completely voluntary.
- That testing is confidential.
- How testing is done.
- When and how results are given.
- What the results means.

- **If patient agrees to have VCCT, refer to the lay counsellor for testing.**
- **If a lay counsellor is not available, refer to health facility where testing is available.**

FOLLOW-UP OF KNOWN HIV-POSITIVE PATIENT

HIV POSITIVE

- Establish a relationship with the patient and encourage regular follow-up.
- Respect his/her right to confidentiality.
- Refer to the lay counsellor should the patient require further counselling.
- Encourage safer-sex practices.
- Provide medical care at each visit.
- Look for and treat HIV-related diseases.

ORAL THRUSH/CANDIDA

Go to page 9

ASYMMETRIC LARGE GLANDS

Refer:
For exclusion of extra-pulmonary TB.

ANY OTHER HIV-RELATED DISEASES

Refer to:
South African Department of Health booklet: Recommendations for the prevention and treatment of opportunistic and HIV-related diseases in adult. (www.http://196.36.153.56/doh/aics/docs/adult.html)

HIV NEGATIVE

Encourage safer sex practices.

WHO IS ELIGIBLE FOR LIFE-LONG COTRIMOXAZOLE (BACTRIM) PROPHYLAXIS? (2 SINGLE STRENGTH TABLETS (80/400MG) PER DAY)

All HIV-infected TB patients.

All symptomatic HIV patients (World Health Organisation (WHO) stage 2,3,4). Refer below.

If previous diagnosis of Pneumocystis carinii pneumonia.

Cotrimoxazole (Bactrim) prophylaxis is started at a higher-level facility.

ADAPTED FROM THE WORLD HEALTH ORGANISATION (WHO) CLINICAL STAGING FOR HIV INFECTION

STAGE 1

Without symptoms.
Acute viral illness following HIV infection.
Persistent swollen glands < 2 cm and symmetrical.

STAGE 2

Unintentional weight loss.
Minor mouth and skin conditions (dry skin, mouth ulcers, fungal nail infections).
Herpes Zoster within the last 5 years.
Recurrent upper respiratory tract infections (eg. sinusitis).

STAGE 3

Significant unintentional weight loss.
Diarrhoea for more than a month.
Fever for more than a month.
Oral thrush/candida.
Pulmonary TB in the last year.
Severe pneumonia or other bacterial infections.
Vaginal candida for more than one month, or poor response to therapy.

STAGE 4

Chronic weight loss plus diarrhoea or fever.
Diagnosed opportunistic infection.
Extra-pulmonary TB.
Kaposi's sarcoma.
HIV dementia.
Diagnosed cancer (eg. Lymphoma).

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Guideline design ***Imago -Visual***

Appendix 6: The PALSA desk blotter

- First page of Appendix 6: Desk blotter with side panels closed.
- Second page of Appendix 6 Desk blotter with side panels opened.

1 RECOGNISE SEVERELY ILL ADULT PATIENTS

LOOK FOR

TEMP ≥ 38 C

ADULT PATIENTS WITH COUGH AND/OR DIFFICULT BREATHING:

DID YOU KNOW?

PEOPLE ARE MORE LIKELY TO STOP SMOKING IF ADVISED TO DO SO BY A HEALTH PROFESSIONAL...

...AND SMOKING MAKES ALL LUNG CONDITIONS WORSE SO TELL YOUR PATIENTS TO QUIT TODAY!

2 SEVERE PATIENTS: START TREATMENT

OXYGEN for all severe patients

ASTHMA /COPD ATTACKS:

- BETA-AGONISTS

via spacer

or

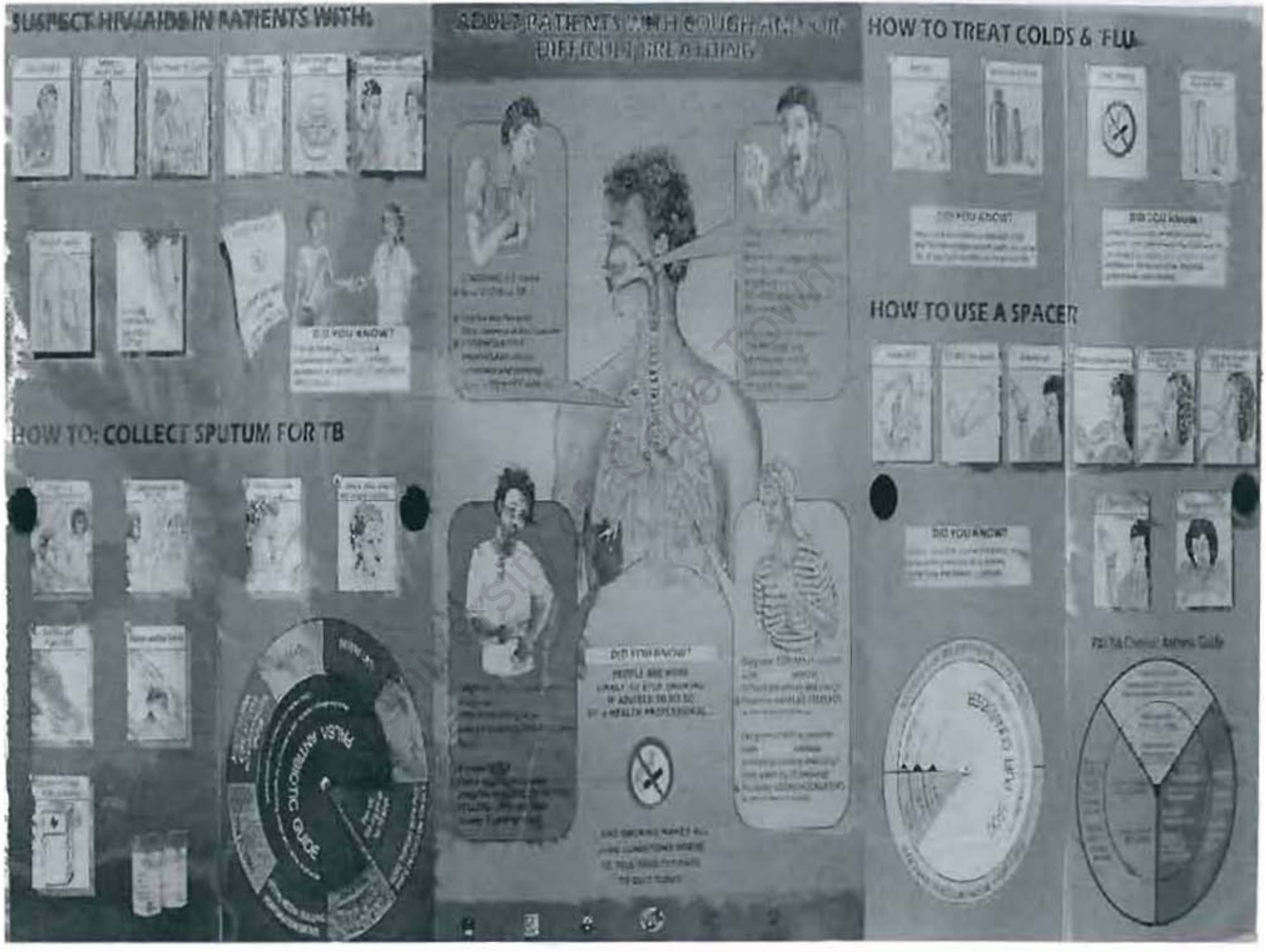
via nebuliser

- PREDNISONE 40mg po stat

SEVERE LRTI:

- AMOXICILLIN 1g po stat

3 & REFER



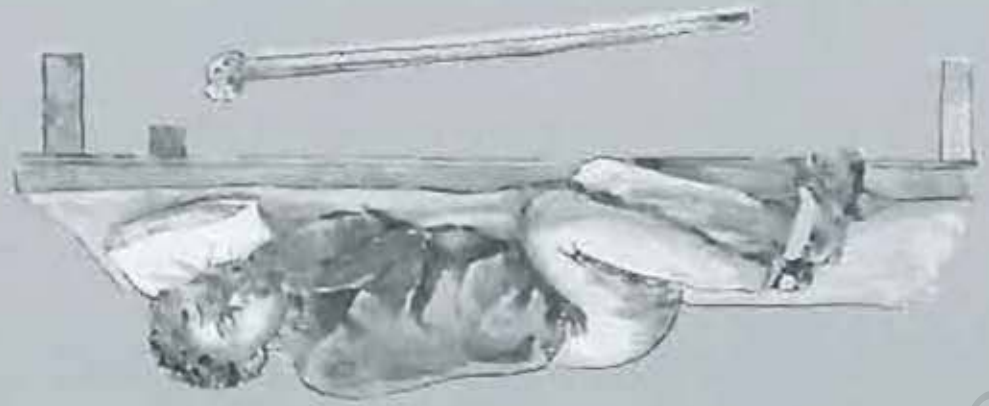
Appendix 7: The PALSA flipchart

PRACTICAL APPROACH TO LUNG HEALTH IN SOUTH AFRICA (PALSA) GUIDELINES


SISTER
FIGHT
TB


SISTER
FIGHT
TB


SISTER
FIGHT
TB




SISTER
FIGHT
TB

COUGHING > 2 weeks
- Send SPUTA for TB
- Test for HIV because TB is common in HIV patients
- COTRIMOXAZOLE PROPHYLAXIS decreases complications and prolongs life in HIV

Diagnose URTI in patients with a blocked or runny nose, sore throat and mild fever but NO difficult breathing or chest pain

Prescribe SYMPTOMATIC TREATMENT only [Antibiotics only if pus on tonsils, in ears or nasal secretions]

Diagnose LRTI in patients with cough, difficult breathing, pain on coughing/breathing and fever

- If severe REFER
- If new or purulent sputum prescribe AMOXICILLIN for 7 days
- FOLLOW - UP in one week (sooner if getting worse)

Diagnose ASTHMA in patients with recurrent wheeze, difficult breathing and cough
- Prescribe INHALED STEROIDS (&refer)

Diagnose COPD in patients with persistent wheeze, difficult breathing and cough (and a history of smoking)
- Prescribe BRONCHODILATORS (& refer)

Appendix 8: The PALSA educational outreach training script (to accompany the guideline, flipchart, and desk blotter)

refer to FLIPCHART

FLIP 1: **Respiratory illness are very common in primary care.**

Here's a typical scenario of a busy primary care clinic. You've got patients streaming through, while others are seated and awaiting nurses' help. Many of these pts. present with difficult breathing (SOB, wheeze, chest-tightness) and/ or cough. These are TYPICAL respiratory symptoms that nurses CAN RECOGNISE in clinics.

How do you identify ADULT pts. who have respiratory illness?

COUGH + DIFFICULT BREATHING are the 2 most common symptoms.

Refer **Page 1** guidelines manual

Nurses should .... SUSPECT respiratory disease in all pts. who present with difficult breathing and/ or cough. Most, and certainly all serious cases, present with cough and difficult breathing.

FLIP 2: **Respiratory illness affects 1 in every 3 patients.**

You've have patients in the waiting room .... The one's in blue.. these patients are presenting with signs of difficult breathing:

SOB, wheeze, chest-tightness and/ or cough.

As you can see respiratory illness is very common. It affects 1 in every 3 pts.

FLIP 3: **Recognise SEVERITY FIRST! Very sick pts. require YOUR immediate care.**

Now that you've identified patients who have difficult breathing and/ or cough in the waiting room you would need to assess the severity of their condition. This would mean that severely ill patients are attended first, and referred.

Severity should be assessed in all patients upon arrival. This patient in red you see here [refer to page...] – requires immediate attention. He requires oxygen and must be referred. When nurses triage, severely ill pts present in two ways.

Respiratory distress, Tight chest	wheeze, shortness of breath→pt. in a state of panic, seeks nurse's attention at consultation room
Moribund	lying down, looking a little wasted, quiet, sleepy, probably sweating, confused → hardly noticeable

How DO you identify SEVERE respiratory illness?
What are the most common indicators used to assess severity?

Nurses are capable of identifying severe resp. illness in the waiting room by looking for key indicators. They should do a quick clinical assessment from observation.

refer Desk blotter 1 LHS FLAP

If the patient is

- **breathing rapidly: ≥ 30 breaths per minute**
- **breathless at rest or while talking**
- **overusing neck muscles**
- **hot : temperature > 38 °C**
- **agitated / confused**
- **coughing blood**

you prescribe treatment AND refer.

Refer **Page 2** guidelines manual

How would you treat a pt. with severe respiratory illness?

refer Desk blotter	**2** RHS FLAP

Treatment of pt. with severe respiratory illness:
Give O_2 to ALL pts to restore breathing.
Ascertain whether the pt. has a *bacterial infection* or suffering an *acute exacerbation.*
How would you do this? Do a quick physical examination. Observe if pt. is:

- Wheezing / tight chest/ Asthma / COPD → give β_2 **agonist** (nebulise / 4-8puffs via spacer) every 20' + **Prednisone** 40 mg (po) stat

Refer **Page 3** guidelines manual

- LRTI /Pneumonia / T ≥ 38 ° C → Give antibiotics:
  Amoxycillin(1g)/ Erythromycin (500 mg) po

Refer **Page 5** guidelines manual

REFER!

FLIP 4: **Now that you've attended to the severe pt. return to the patient presenting with chronic respiratory symptoms. Diagnose and treat**

How would you know if a pt. has pneumonia? or TB? URTI? or LRTI
How are you able to differentiate between upper and lower respiratory tract infection?
What are the key signs that nurses should look for?
How do you differentiate between upper and lower respiratory symptoms?

Overview of 4 respiratory diseases
We have outlined the 4 common respiratory diseases that nurses are most likely to encounter in their clinics. We've provided the most common indicators to help nurses make a diagnosis and provide the appropriate treatment.

TB

Suspect TB in all pts. with

- **Cough for >2 weeks**
- **Night sweats, fever**
- **Weight loss, loss of appetite**
- **Blood stained sputa**
- **HIV +**

Sputa Collection: How do nurses collect sputa?
Nurse + pt. stand in well ventilated room - perhaps outside. Nurse does **NOT stand in front** of pt.
Pt. rinses mouth, takes a deep breath + coughs forcibly into sputum jar.
Nurse replaces and tightens the lid.
Nurse washes her hand under running water.

Sputum labeled and stored in fridge for collection

Label bottles on the days that sputa were collected
Schedule follow –up → TB can be cured!

HIV is common in TB pts

Nurses should encourage pts. to TEST for HIV because ....
Co-trimoxazole Prophylaxis = 2 tabs (80/400) daily ↓ complications; prolongs life.

Prophylaxis eligibility Refer **Page 22** guidelines manual

- HIV infected TB pts.
- Dx. of pneumocystis carinii pneumonia
- Symptomatic HIV stages (WHO staging 2,3,4)

Suspect / THINK about HIV/ AIDS in pts. with Refer **Page 6** guidelines manual

- TB
- Oral thrush =white patches, scratched off with difficulty → bleeding (Pg 6)
- Herpes zoster= painful rash with blisters confined to 1 part of the body
- Recurrent URTI = colds, flu
- Long Hx of diarrhoea > 3 wks + severe wt. loss
- STIs
- Painless swollen glands
- High risk sexual behaviour

Encourage VCCT → completely confidential + voluntary

Teach about HIV/AIDS, methods of transmxn, avoidance of high-risk behaviour

What the test results means?
Who does the test?
How testing is done?
When, how results are given

If Pt . agrees → refer to lay counsellor / to health facility

Follow-up of HIV +

Encourage follow-up care, safe-sex practice
Respect confidentiality
Refer to lay counsellor
Medical care @ each visit
Look for signs of: Oral thrush
Asymmetric large swollen glands

URTI

Refer **Pages 6 –10** guidelines manual

Diagnose URTI if

- **blocked or runny noses**
- **sneezing**

- **sore throat**
- **mild fever**

NO difficult breathing + NO chest pain

Pts. with flu have MYALGIA; those without it have a common cold
Most colds + flus last for 3-5 days.

Treatment **NO pus = NO fuss → NO antibiotics**

Most URTIs = viral → NO antibiotics! Antibiotics are only effective for bacterial infections and make NO difference for colds and flus

Symptomatic: Bed rest, Drink plenty clear fluids

ALLERGIC RHINITIS Refer **Page 6** guidelines manual

Intermittent — Antihistamine: **chlorpheniramine**
NaCl nose drops

Persistent — Refer → steroid nasal spray

SINUSITIS Refer **Page 7** guidelines manual

Mild : Post nasal drip, clear nasal discharge **Oxymetazoline**, NaCl drops

Severe: pussy nasal discharge — **Amoxycillin / Co-trimoxazole**
facial/ tooth pain — Refer → swelling around eye
symptoms > 7 days — tooth abscess

PHARYNGITIS Refer **Page 8** guidelines manual

red throat *without* pus — salt water m/wash; paracetamol
red throat *with* pus, white patches on tonsils (=b/tonsillitis) — **Pen VK / Erythromycin**
CANDIDA (thrush = white patches in mouth) — **Nystatin**

EAR Refer **Page 10** guidelines manual

Inflammed /infected *outer ear:*
*d*ischarging + swollen *ear canal* — **Flucloxacillin/ Erythromycin**
acetic acid ear drops+ dry mop

Bulging/ perforated/ pussy *eardrum* < 2wk — **Amoxycillin / Co-trimoxazole**
Chronic — dry mop, refer

Ask trainers:

What would you do if there is pus discharging from the ear?
What simple approach would you use to get rid of pus from the ear?

Dry mop

Roll piece of cotton wool into wick
Leave in ear; remove once wick is wet
Repeat 4x daily until ear is dry
Never leave wick / objects in the ear

Asthma + COPD

Refer **Page 12** guidelines manual

Most often symptoms for both conditions are quite similar and it is difficult to tell them apart from each other. To help nurses **differentiate** between them they should take a

medical history to arrive at a more definite conclusion.

Diagnose ASTHMA if pt.has:

- **recurrent** WHEEZE ✔
- difficult breathing AND cough ✔

Ask if : Symptoms started in childhood? / adulthood? ✔
Family history of asthma? ✔
Intervals of normal breathing? ✔
Symptoms worsen at night, early hrs. of the morning? ✔
Symptoms improve / disappear after using pump? ✔
Symptoms only present at work? ✔

Treatment: INHALED STEROIDS + inhaled bronchodilator
Beclomethasone = Viarox®, Beclate®,
Budenoside = Inflammide®,

Diagnose COPD if:

- **persistent** WHEEZE ✔
- difficult breathing AND cough ✔
- **history of smoking** ✔

Asthma (recurrent)	***COPD (persistent)***
Starts in childhood /early adulthood	Starts in **adulthood** (>35), worsen over time
Hx of hayfever,eczema, allergies, family hx	Hx of heavy **smoking** (> 20 cigarettes/day)
Symptoms only during **attacks** with periods of normal breathing	SOB for **most** of the day. Daily cough Sputum prodn. starts long before SOB
Worse at **night**; early morning; during a cold, weather changes; when @ **work**	

Poorly controlled asthma if pts. are

- awakened at night frequently because of asthma
- using a bronchodilator frequently > 4xdaily

Treatment: Oral Prednisone 40 mg daily x 14 days

Check pts. inhaler technique. **Recommend SPACER**

Shake MDI
Fit MDI into spacer
Breathe out
Press down the pump once
Immediate inhale from spacer mouthpiece
Hold breath, count to 10
Breathe out
Rinse mouth
Spacers carry a static electricity charge that causes drug to stick to the spacer wall.
WASH spacer once a month (not everyday) using washing up liquid and allow it to drip dry.

COPD Refer **Page 14** guidelines manual

COPD pts. have a history of cigarette smoking. Encourage pts. to stop smoking!

Document tobacco use
Determine willingness to quit
Suggest ways to reduce smoking
Schedule follow-up visit

Assess severity of breathlessness during activity	**Inhaled salbutamol /ipratropium bromide**
Infection (sputum =purulent, / color change to yellow /green)	**Amoxycillin / Erythromycin + Prednisone 40mg**
Ankle oedema (RHF)	Refer → Diuretics

LRTI pneumonia

Refer **Page 5** guidelines manual

Diagnose if

- Cough + Difficult breathing
- **Chest pain on breathing / cough**
- Fever

SEVERE → Refer

Treatment

New/ or ↑ sputa prodn +colour change: **Amoxycillin / Erythromycin**
NO Smoking
High fluid intake
Paracetamol
Follow-up after 1 wk

Exclude TB: cough ≥ 2 weeks, loss of wt, night sweats, blood stained sputum, HIV

FLIP ... SMOKING worsens lung diseases. More people stop smoking if encouraged by a health care professional. Smoking makes *all* respiratory conditions worse.

Nurses + Drs who encourage patients to quit smoking actually do so! Quit smoking today.

Remind pts. about the hazards of smoking on every visit.

- identify and document all tobacco use at each visit
- strongly urge pt. to quit
- determine willingness to quit
- help the pt. to quit
- schedule follow-up contact

Appendix 9: Consent forms for persons ≥ 18years and < 18 years

PATIENT INFORMATION AND WRITTEN CONSENT FORM – PALSA VALIDATION STUDY (PATIENTS 12 YEARS AND UP TO AND INCLUDING 17 YEARS OF AGE)

Screening Number: S _ _ _ _
Study Number: _ _ _ _
Patient's Initials: _____

Your child is invited to participate in a research project. Before you agree to allow your child to participate you need to understand what it involves.

Purpose of study

Researchers from the UCT Lung Institute and Medical Research Council are studying patients who present to the Community Health Clinic with a complaint of difficult breathing and/or cough.

The reason for doing this study is to test a new clinic plan to improve the treatment of respiratory diseases. We aim to see how well nurses can diagnose respiratory diseases using this new guideline.

Do I have to participate in this study?

Your child's participation in this study is voluntary. If you agree to allow him/her to take part, we require of you to sign this form. You are free to withdraw him/her from the study at any stage and this will in no way affect the way in which your child will be treated in the clinic today. Likewise, should we feel that further participation in the study would not be in your child's best interest we will withdraw him/her from the study.

What will happen to me if I participate?

The process may take longer than usual (usually less tan 2 hours). First, your child will be seen by a nurse who will record information about his/her medical history and current condition. She may record your child's temperature, and will examine him/her. Thereafter, your child will be escorted to another cubicle where he/she will be examined by a doctor. Information regarding medical history and their current condition will also be recorded. His/her blood pressure, temperature, weight, height, oxygen levels in the blood and lung function will be measured. In addition a chest x-ray may be done. If blood tests are considered advisable the reasons will be explained to you and your child and your further consent will be requested.

What are the possible drawbacks or discomforts in participating in this study?

Drawing of the blood samples may cause some discomfort. His/her stay at the community health centre may be longer than would have expected it to be.

What are the possible benefits of participating in this study?

The information that we obtain from the study will help us improve the diagnosis and treatment of respiratory diseases by nurses at primary health care in South Africa.

Will the information remain confidential?

Should you agree to allow your child to participate in the study all his/her records will be viewed by the study investigators and by a specialist physician. Their information will not be viewed by any other persons or parties not involved in this study. All the information will be safely stored on a computer and at the study site. At no time will anyone be able to link the information stored on the computer to your name.

Contact details of the study staff

Should you have any questions about the study, please ask any of the following research team.

Name _____ Phone Number _____

Name _____ Phone Number _____

WRITTEN INFORMED CONSENT FORM FOR PARENT OR LEGAL GUARDIAN

Screening Number: S _ _ _ _
Study Number: _ _ _ _
Patient's Initials: _____

I,.....
(Name of Patient and parent or legal guardian in block letters)

have read and understood all the information given to me about my child's participation in this study and I have been given the opportunity to discuss it and ask questions. I voluntarily agree to allow my child to participate in this study and understand that I will receive a copy of this consent form.

....
Signature of Parent or legal guardian Date

.....
Printed name of Parent or legal guardian

....
Signature of Patient (if possible) Date

.....
Printed name of Patient

I have explained the nature and purpose of the study to the Patient and Parent or legal guardian named above.

....
Signature of Principal Investigator or delegate Date

.....
Printed name of Principal Investigator or delegate

WRITTEN INFORMED CONSENT FORM FOR PATIENT REPRESENTATIVE

Screening Number: S _ _ _ _
Study Number: _ _ _ _
Patient's Initials: _____

I,.....
(Name of Patient and parent or legal guardian in block letters)

have read and understood all the information given to me about my child's participation in this study and I have been given the opportunity to discuss it and ask questions. I voluntarily agree to allow my child to participate in this study and understand that I will receive a copy of this consent form.

....
Signature of patient representative Date

.....
Printed name of patient representative

....
Signature of Patient (if possible) Date

.....
Printed name of Patient

I have explained the nature and purpose of the study to the Patient and Parent or legal guardian named above.

....
Signature of Principal Investigator or delegate Date

.....
Printed name of Principal Investigator or delegate

PATIENT INFORMATION AND WRITTEN CONSENT FORM – PALSA VALIDATION STUDY (PATIENTS 18 YEARS AND OLDER)

Screening Number: S _ _ _ _
Study Number: _ _ _ _

Patient's Initials: _____

You are invited to participate in a research project. Before you agree to take part you need to understand what it involves.

Purpose of study

Researchers from the UCT Lung Institute and Medical Research Council are studying patients who present to the Community Health Clinic with a complaint of difficult breathing and/or cough.

The reason for doing this study is to test a new clinic plan to improve the treatment of respiratory diseases. We aim to see how well our nurses can diagnose respiratory diseases using this new guideline.

Do I have to participate in this study?

Your participation in this study is voluntary. If you agree to take part, we require of you to sign this form. You are free to withdraw from the study at any stage and this will in no way affect the way that you will be treated in the clinic today.

What will happen to me if I participate?

The consultation process may take a little longer than usual (usually less than 3 hours)). First, you will be seen by a nurse who will record information about your medical history and current condition. She may record your temperature, and will examine you. Thereafter, you will be escorted to another cubicle where you will be examined by a doctor. Information regarding your medical history and current condition will also be recorded. Your blood pressure, temperature, weight, height, oxygen levels in the blood and lung function will be measured. In addition a chest x-ray may be done. If blood tests are considered advisable the reasons will be explained to you and your further consent will be requested.

What are the possible drawbacks or discomforts in participating in this study?

Drawing of the blood samples may cause some discomfort. Your stay at the community health centre may be longer than you would expect it to be.

What are the possible benefits of participating in this study?

The information that we obtain from the study will help us improve the diagnosis and treatment of respiratory diseases by nurses at primary health care clinics in South Africa.

Will the information remain confidential?

Should you agree to participate in the study all your records will be viewed by the study investigators and a specialist physician. Your information will not be viewed by any other persons or parties not involved in this study. All the information will be safely stored on a computer and at the study site. At no time will anyone be able to link the information stored on the computer to your name.

Contact details of the study staff

Should you have any questions about the study, please ask any of the following research members.

Name _____ Phone Number _____

Name _____ Phone Number _____

WRITTEN INFORMED CONSENT FORM FOR PATIENT

Screening Number: S _ _ _ _
Study Number: _ _ _ _
Patient Initials: _____

I,.....
(Name of Patient in block letters)

have read and understood all the information given to me about my participation in this study and I have been given the opportunity to discuss it and ask questions. I voluntarily agree to take part in this study and understand that I will receive a copy of this consent form.

....
Signature of Patient Date

.....
Printed name of Patient

I have explained the nature and purpose of the study to the Patient named above.

....
Signature of Principal Investigator or delegate Date

.....
Printed name of Principal Investigator or delegate

WRITTEN INFORMED CONSENT FORM FOR PATIENT REPRESENTATIVE

Screening Number: S _ _ _ _
Study Number: _ _ _ _
Patient Initials: _____

.....
(Name of Patient)

has understood all the information given to him/her about this study and has been given the opportunity to discuss it and ask questions. This patient has voluntarily agree to take part in this study and understands that he/she will receive a copy of this consent form.

....
Signature of Patient Representative Date

.....
Printed name of Patient Representative

I have explained the nature and purpose of the study to the Patient named above.

....
Signature of Principal Investigator or delegate Date

.....
Printed name of Principal Investigator or delegate

Appendix 10: Nurse record form

PATIENT NOTES FOR PALSA NURSE

Screening no:_____
Study no: _____
Initials: _____

Weight: _____ Sats: _____ Occupation: _____
Height: _____ BP: _____ Gender: _____
Temp: _____ Pulse: _____ Smoking History: _____
RR: _____

Known Medical Conditions:

1) _____
2) _____
3) _____
4) _____

Current Medication:

1) _____
2) _____
3) _____
4) _____
5) _____
6) _____

History, symptoms and signs:

_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____
_____

Comments:

_____
_____
_____
_____
_____
_____

Appendix 11: Doctor record form

Appendix 12: Specialist record form

FINAL DIAGNOSIS

(This form is to be completed by the Specialist Physician. File in the SPECIALIST PHYSICIAN'S FILE.)

SCREENING NUMBER: S _ _ _ _ **STUDY NUMBER: _ _ _ _**

PATIENT INITIALS _____ **DATE: _ _ /_ _ /2 0 0**

FINAL DIAGNOSIS:

_____

_____

_____

_____

PRIMARY PALSA CATEGORY: _____

CERTAINTY OF DIAGNOSIS: 1 ----------5

SECONDARY PALSA CATEGORY: _____

CERTAINTY OF DIAGNOSIS: 1 ----------5

TERTIARY CATEGORY: _____

CERTAINTY OF DIAGNOSIS: 1 ----------5

QUARTENARY PALSA CATEGORY: _____

CERTAINTY OF DIAGNOSIS: 1 ----------5

PROPOSED MANAGEMENT PLAN:

_____

_____

_____

_____

COMMENTS:

_____

_____

_____

_____

_____

_____

REVIEW NEEDED: YES ☐ NO ☐

REVIEWED BY DR/PROF _____

Appendix 13: Table listing key messages and barriers

Diseases and Corresponding key messages	Barrier Addressed	Source data	Form of Key messages
TB and HIV			
Coughing ≥ 2 weeks. Send sputa for TB. - test for HIV because TB is common in HIV patients. - Cotrimoxazole prophylaxis delays symptoms and prolongs healthy life in HIV patients.	Knowledge	Brainstorming, focus group discussions	Directive in words
Sputum collection	Knowledge and skills	Focus group discussions	Visual: (cartoon or other graphic)
Suspecting HIV/AIDS in patients with TB	Knowledge and skills	Focus group discussion	Visual (cartoon or graphic)
OBSTRUCTIVE LUNG DISEASE			
Diagnose asthma in patients with recurrent wheeze, difficult breathing and cough. - Prescribe inhaled corticosteroids (and refer for doctor follow-up). Diagnose COPD in patients with persistent wheeze, difficult breathing and cough (and a history of smoking. - Prescribe bronchodilators (and refer for doctor follow-up).	Knowledge and skills Physical resources	Brainstorming, focus group discussion.	Directive
Instructions on how to use a spacer	Knowledge and skills	Brainstorming, focus group discussion, lit.	Visual: (cartoon or other graphic)
Spacers should be used with inhaled steroids because they increase drug delivery to the lung and reduce oral thrush	Knowledge and skills	Brainstorming, focus group discussion, lit.	Question prompt: ("did you know..?")
Dose-puff converter	Knowledge and skills	Brainstorming, focus group discussion, lit.	Gimmick: (Special aid)
Asthma diagnostic guide	Knowledge and skills	Brainstorming, focus group discussion, lit.	Gimmick: (Special aid)
RESPIRATORY TRACT INFECTIONS			
Diagnose LRTI in patients with: cough, plus difficult breathing, and/or pain on coughing/breathing and or fever - If sever, refer. - In new or purulent sputum prescribe amoxicillin for 7 days. - Follow-up in one week (sooner if getting worse) Diagnose URTI in patients with: Bocked or runny noses, and/or Sore throats, and/or Mild fever but No difficult breathing No chest pain - Prescribe symptomatic treatment only [antibiotics only if pus on tonsils, in ears or nasal secretions.]	Knowledge and skills	Brainstorming, focus group discussion, lit.	Directive in words
Instructions on how to treat colds and flu	Knowledge and skills	Brainstorming, focus group discussion, lit	Visual: (cartoon or other graphic)
Reinforcing the differences between colds and flu	Knowledge and skills	Brainstorming, focus group discussion, lit.	Question prompt: ("did you know..?")
Reinforcing that antibiotics are not to be prescribed for colds and flu.	Knowledge and skills	Brainstorming, focus group discussion, lit.	Question prompt: ("did you know?")